PALM INTRANET

Day : Friday
Date: 11/10/2006
Time: 12:34:45

Inventor Information for 10/801729

Inventor Name	City	State/Country
KAO, PETER N.	PALO ALTO	CALIFORNIA
PEARL, RONALD G.	PALO ALTO	CALIFORNIA
NISHIMURA, TOSHIHIKO	MENLO PARK	CALIFORNIA
FAUL, JOHN L.	STANFORD	CALIFORNIA

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign Data | Invento

Search Another: Application# [ ] Search **or Patent#** [ ] Search

PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

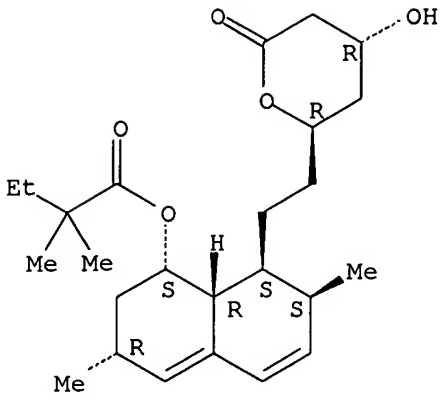
Bar Code # [ ] Search

To go back use Back button on your browser toolbar.

Back to PALM | ASSIGNMENT | OASIS | Home page

L1 ANSWER 17 OF 17 REGISTRY COPYRIGHT 2006 ACS on STN
RN 79902-63-9 REGISTRY
ED Entered STN: 16 Nov 1984
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanoic acid, 2,2-dimethyl-, 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[1α,3α,7β,8β(2S*,4S*),8aβ]]-
OTHER NAMES:
CN **(+)-Simvastatin**
CN Cholestat
CN Denan
CN Eucor
CN Kolestevan
CN L 644128-000U
CN Lipex
CN Lipinorm
CN Liponorm
CN Lipovas
CN Lodales
CN MK 733
CN Modutrol
CN Nor-Vastina
CN Rechol
CN Simcor
CN Simovil
CN **Simvastatin**
CN **Simvastatin lactone**
CN Simvotin
CN Sinvacor
CN Sinvascor
CN Sivastin
CN Statin
CN Synvinolin
CN Valemia
CN Velostatin
CN Zocor
CN Zocord
FS STEREOSEARCH
DR 98609-43-9, 118607-03-7
MF C25 H38 O5
CI COM
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CHEMCATS, CIN, CSCHEM, CSNB, DDFU, DRUGU, EMBASE, HSDB*, IFICDB, IFIUDB, IMSCOSEARCH, IMSDRUGNEWS, IMSPATENTS, IMSRESEARCH, IPA, MEDLINE, MRCK*, NAPRALERT, PATDPASPC, PHAR, PROMT, PROUSDDR, PS, RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: WHO

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

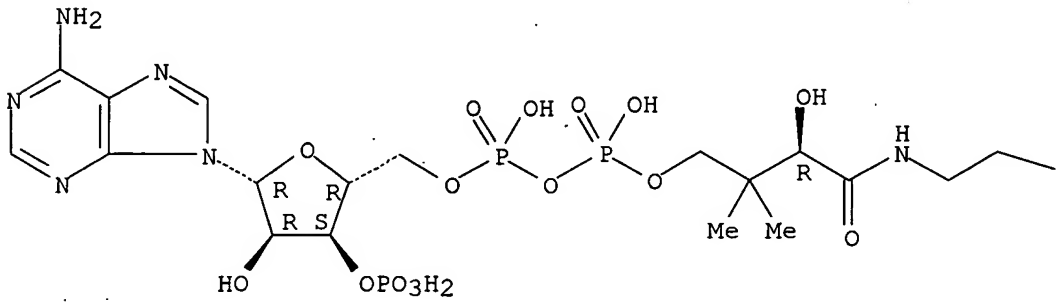
3304 REFERENCES IN FILE CA (1907 TO DATE)
79 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3317 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

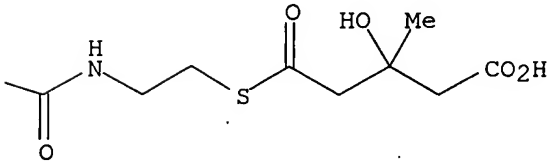
L2 ANSWER 68 OF 68 REGISTRY COPYRIGHT 2006 ACS on STN
RN 1553-55-5 REGISTRY
ED Entered STN: 16 Nov 1984
CN Coenzyme A, S-(hydrogen 3-hydroxy-3-methylpentanedioate) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Coenzyme A, S-(hydrogen 3-hydroxy-3-methylglutarate) (8CI)
OTHER NAMES:
CN β-Hydroxy-β-methylglutaryl CoA
CN β-Hydroxy-β-methylglutaryl-coenzyme A
CN 3-Hydroxy-3-methylglutaryl CoA
CN 3-Hydroxy-3-methylglutaryl coenzyme A
CN **HMG-CoA**
CN Hydroxymethylglutaryl CoA
CN Hydroxymethylglutaryl coenzyme A
FS STEREOSEARCH
DR 13351-03-6, 25828-49-3
MF C27 H44 N7 O20 P3 S
CI COM
LC STN Files: ADISNEWS, AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CHEMLIST, CIN, CSCHEM, EMBASE, IFICDB, IFIUDB, MEDLINE, PROMT, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

407 REFERENCES IN FILE CA (1907 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
409 REFERENCES IN FILE CAPLUS (1907 TO DATE)
3 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

```
FILE 'CAPLUS' ENTERED AT 13:37:22 ON 10 NOV 2006
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 13:37:22 ON 10 NOV 2006

FILE 'BIOSIS' ENTERED AT 13:37:22 ON 10 NOV 2006
Copyright (c) 2006 The Thomson Corporation

FILE 'EMBASE' ENTERED AT 13:37:22 ON 10 NOV 2006
Copyright (c) 2006 Elsevier B.V. All rights reserved.

=> s l6
L7       17401 L6

=> s l7 and (pulmonary or lung or bronchial or bronch? or eisenmenger or
lymphangioleiomyomatosis or thromboembo?)
L8         417 L7 AND (PULMONARY OR LUNG OR BRONCHIAL OR BRONCH? OR EISENMENGE
               R OR LYMPHANGIOLEIOMYOMATOSIS OR THROMBOEMBO?)

=> s simvastatin or 79902-63-9/rn or zocor
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
'RN' IS NOT A VALID FIELD CODE
L9       22437 SIMVASTATIN OR 79902-63-9/RN OR ZOCOR

=> s l9 and l8
L10        113 L9 AND L8

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11         105 DUP REM L10 (8 DUPLICATES REMOVED)

=> focus
PROCESSING COMPLETED FOR L11
L12         105 FOCUS L11 1-

=> s l12 and (pulmonary adj hypertension)
L13           0 L12 AND (PULMONARY ADJ HYPERTENSION)

=> s l12 and (hypertension)
L14         38 L12 AND (HYPERTENSION)

=> s l14 and (pulmonary or lung)
L15         36 L14 AND (PULMONARY OR LUNG)

=> focus
PROCESSING COMPLETED FOR L15
L16          36 FOCUS L15 1-

=> d ibib abs 1-36 hitstr

L16  ANSWER 1 OF 36  CAPLUS  COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER:        2005:474950  CAPLUS
DOCUMENT NUMBER:         143:1287
TITLE:                   Use of antiproliferative agents in the treatment and
                         prevention of pulmonary proliferative
                         vascular diseases
INVENTOR(S):             Kao, Peter N.; Pearl, Ronald G.; Nishimura, Toshihiko;
                         Faul, John L.
PATENT ASSIGNEE(S):      USA
```

SOURCE: U.S. Pat. Appl. Publ., 30 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005119330	A1	20050602	US 2004-801729		20040315
PRIORITY APPLN. INFO.:			US 2003-455470P	P	20030317

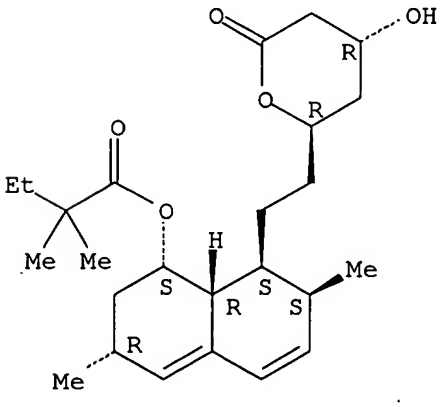
AB Methods of treating **lung** proliferative vascular disorders by administering an antiproliferative agent are provided. A preferred antiproliferative agent is a HMG-CoA reductase inhibitor, preferably **simvastatin**. Vascular occlusion in the **pulmonary** arteries of the patient is reduced as a result of the treatment through a reduction in neointimal hyperplasia and medial hypertrophy, and the restoration of normal endothelial cell function. The treatment also results in a reversal of right side cardiac hypertrophy. **Lung** proliferative vascular disorders that can be treated include primary **pulmonary hypertension**, secondary **pulmonary hypertension**, **Eisenmenger**'s syndrome, chronic **thromboembolic** disease, **pulmonary** fibrosis, obliterative **bronchiolitis**, or **lymphangioleiomyomatosis**. Dosages and pharmaceutical formulations are provided.

IT **9028-35-7**, 3-Hydroxy-3-methylglutaryl Co A reductase
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor; use of antiproliferative agents in treatment and prevention of **pulmonary** proliferative vascular diseases)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of antiproliferative agents in treatment and prevention of **pulmonary** proliferative vascular diseases)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 2 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1278427 CAPLUS
DOCUMENT NUMBER: 144:32081
TITLE: **Simvastatin** enhances bone morphogenetic protein receptor type II expression
AUTHOR(S): Hu, Hong; Sung, Arthur; Zhao, Guohua; Shi, Lingfang; Qiu, Daoming; Nishimura, Toshihiko; Kao, Peter N.
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Stanford University Medical Center, Stanford, CA, 94305-5236, USA
SOURCE: Biochemical and Biophysical Research Communications (2006), 339(1), 59-64
CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

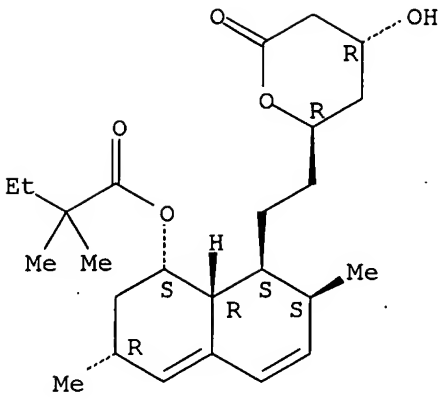
AB Statins confer therapeutic benefits in systemic and **pulmonary** vascular diseases. Bone morphogenetic protein (BMP) receptors serve essential signaling functions in cardiovascular development and skeletal morphogenesis. Mutations in BMP receptor type II (BMPR2) are associated with human familial and idiopathic **pulmonary** arterial **hypertension**, and pathol. neointimal proliferation of vascular endothelial and smooth muscle cells within small **pulmonary** arteries. In severe exptl. **pulmonary hypertension**, **simvastatin** reversed disease and conferred a 100% survival advantage. Here, modulation of BMPR2 gene expression by **simvastatin** is characterized in human embryonic kidney (HEK) 293T, **pulmonary** artery smooth muscle, and **lung** microvascular endothelial cells (HLMVECs). A 1.4 kb BMPR2 promoter containing Egr-1 binding sites confers reporter gene activation in 293T cells which is partially inhibited by **simvastatin**. **Simvastatin** enhances steady-state BMPR2 mRNA and protein expression in HLMVEC, through posttranscriptional mRNA stabilization. **Simvastatin** induction of BMPR2 expression may improve BMP-BMPR2 signaling thereby enhancing endothelial differentiation and function.

IT **9028-35-7**, NADPH-hydroxymethylglutaryl-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, statins; **simvastatin** enhances bone morphogenetic protein receptor type II expression)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**simvastatin** enhances bone morphogenetic protein receptor type II expression)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 3 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:605412 CAPLUS
DOCUMENT NUMBER: 141:134086
TITLE: Telmisartan-**simvastatin** combination for prophylaxis or therapy of cardiovascular, cardiopulmonary, **pulmonary**, or renal diseases
INVENTOR(S): Riedel, Axel; Sendra, Josep-Maria; Leiter, Josef M. E.
PATENT ASSIGNEE(S): Boehringer Ingelheim Pharma GmbH & Co. Kg, Germany
SOURCE: Ger. Offen., 10 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10301372	A1	20040729	DE 2003-10301372	20030116
AU 2004204353	A1	20040729	AU 2004-204353	20040114
CA 2513281	AA	20040729	CA 2004-2513281	20040114
WO 2004062729	A1	20040729	WO 2004-EP175	20040114
WO 2004062729	C1	20041007		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA				
US 2005004193	A1	20050106	US 2004-757015	20040114
EP 1587584	A1	20051026	EP 2004-701918	20040114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004006812	A	20051227	BR 2004-6812	20040114
CN 1738665	A	20060222	CN 2004-80002405	20040114
JP 2006515877	T2	20060608	JP 2006-500558	20040114
NO 2005003793	A	20050810	NO 2005-3793	20050810

PRIORITY APPLN. INFO.:		
DE 2003-10301372	A	20030116
US 2003-446437P	P	20030211
DE 2003-10335027	A	20030731
US 2003-503317P	P	20030916
WO 2004-EP175	W	20040114

AB The invention discloses a pharmaceutical combination for prophylaxis or therapy of cardiovascular, cardiopulmonary, **pulmonary** or renal diseases through improvement of the endothelial function and achievement of a protection of organs, tissue and vessels during indications, with

which blood pressure control and lipid level control is necessary. The invention also discloses a method for the prophylaxis or therapy of these diseases, which require combined administration of effective quantities of defined active substances in such a relationship, which results in an additive and synergistic effect. Furthermore the invention concerns the combined use of these compds. for the production of appropriate pharmaceutical combination prepns. The methodol. of the invention uses **simvastatin** and telmisartan or polymorphs or salts thereof. Preparation of the sodium salt of telmisartan is described.

IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(telmisartan-**simvastatin** combination for prophylaxis or therapy of cardiovascular, cardiopulmonary, **pulmonary**, or renal diseases)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

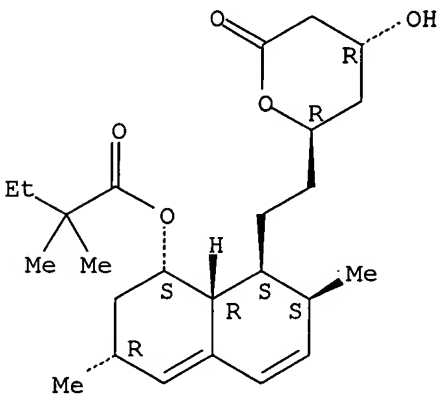
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(telmisartan-**simvastatin** combination for prophylaxis or therapy of cardiovascular, cardiopulmonary, **pulmonary**, or renal diseases)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 4 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2004:610104 CAPLUS

DOCUMENT NUMBER: 141:134092

TITLE: Telmisartan-**simvastatin** combination for the prophylaxis or treatment of cardiovascular, cardiopulmonary, **pulmonary**, or renal diseases

INVENTOR(S): Riedel, Axel; Sendra, Josep-Maria; Leiter, Josef M. E.; Kauschke, Stefan; Mark, Michael

PATENT ASSIGNEE(S): Boehringer Ingelheim International GmbH, Germany; Boehringer Ingelheim Pharma GmbH & Co. Kg

SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: German
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004062729	A1	20040729	WO 2004-EP175	20040114
WO 2004062729	C1	20041007		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA				
DE 10301372	A1	20040729	DE 2003-10301372	20030116
DE 10335027	A1	20050217	DE 2003-10335027	20030731
AU 2004204353	A1	20040729	AU 2004-204353	20040114
CA 2513281	AA	20040729	CA 2004-2513281	20040114
US 2004259925	A1	20041223	US 2004-757295	20040114
EP 1587584	A1	20051026	EP 2004-701918	20040114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2004006812	A	20051227	BR 2004-6812	20040114
JP 2006515877	T2	20060608	JP 2006-500558	20040114
AU 2004260606	A1	20050210	AU 2004-260606	20040724
CA 2534006	AA	20050210	CA 2004-2534006	20040724
EP 1651213	A1	20060503	EP 2004-763484	20040724
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				
CN 1829511	A	20060906	CN 2004-80022096	20040724
BR 2004013165	A	20061003	BR 2004-13165	20040724
NO 2005003793	A	20050810	NO 2005-3793	20050810
NO 2006000938	A	20060227	NO 2006-938	20060227

PRIORITY APPLN. INFO.:			
	DE 2003-10301372	A	20030116
	DE 2003-10335027	A	20030731
	DE 2003-10301371	A	20030116
	US 2003-446695P	P	20030211
	US 2003-503317P	P	20030916
	DE 2003-10346260	A	20031006
	DE 2003-10356815	A	20031205
	WO 2004-EP175	W	20040114
	WO 2004-EP8326	W	20040724

AB The invention discloses a method for the prophylaxis or treatment of cardiovascular, cardiopulmonary, **pulmonary** or renal diseases, achieved by the improvement of endothelial function and the protection of organs, tissues and vessels when indications require a blood pressure check and a lipid level check, especially in patients that have been diagnosed with type 2 diabetes mellitus or if prediabetes is suspected. The method is also used for preventing diabetes and prediabetes and for the treatment of metabolic syndrome and insulin resistance in patients with normal blood pressure. The method involves the combined administration of effective quantities of telmisartan, or a polymorph or salt thereof, and **simvastatin**. The invention also discloses suitable pharmaceutical compns. containing telmisartan, or a polymorph or salt thereof, and **simvastatin**, as a combined preparation for simultaneous, sep., or sequential use in the prophylaxis or treatment of the above diseases. Preparation of the sodium salt of telmisartan is described.

IT **9028-35-7**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (telmisartan-**simvastatin** combination for prophylaxis and treatment of cardiovascular, cardiopulmonary, **pulmonary**, and renal diseases)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

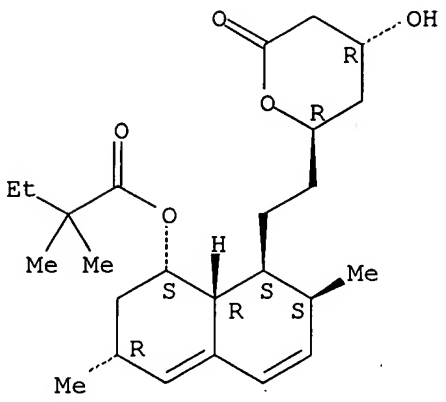
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(telmisartan-**simvastatin** combination for prophylaxis and treatment of cardiovascular, cardiopulmonary, **pulmonary**, and renal diseases)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 5 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:982167 CAPLUS
DOCUMENT NUMBER: 145:348597
TITLE: Use of phenylmethimazoles, methimazole derivatives, and tautomeric cyclic thiones for the treatment of autoimmune/inflammatory diseases associated with toll-like receptor overexpression
INVENTOR(S): Kohn, Leonard D.; Harii, Norikazu; Benavides-Peralta, Uruguaysito; Gonzalez-Murguiondo, Mariana; Lewis, Christopher J.; Napolitano, Giorgio; Giuliani, Cesidio; Malgor, Ramiro; Goetz, Douglas J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 102pp., Cont.-in-part of U.S. Ser. No. 912,948.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006211752	A1	20060921	US 2005-130922	20050517
US 2005209295	A1	20050922	US 2004-801986	20040316
US 2006058365	A1	20060316	US 2004-912948	20040806
PRIORITY APPLN. INFO.:			US 2004-801986 A2	20040316
			US 2004-912948 A2	20040806

AB The present invention relates to the treatment of autoimmune and/or inflammatory diseases associated with overexpression of Toll-like receptor 3 (TLR3) as well as Toll-like receptor 4 (TLR4) and/or TLR3/TLR4 signaling in nonimmune cells, monocytes, macrophages, and/or dendritic cells in

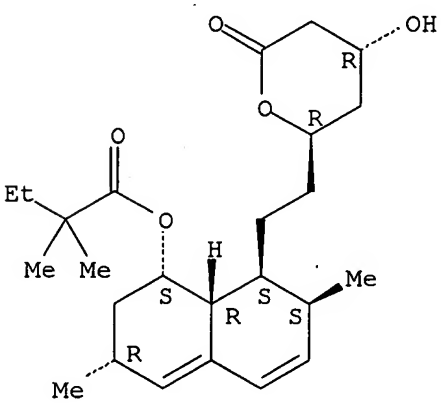
association with related pathologies. This invention also relates to the use of phenylmethimazoles, methimazole derivs., and tautomeric cyclic thiones for the treatment of autoimmune and inflammatory diseases associated with Toll-like receptor 3 (TLR3) as well as Toll-like receptor 4 (TLR4) and/or TLR3/TLR4 signaling in nonimmune cells, monocytes, macrophages, and/or dendritic cells in association with related pathologies. This invention also relates to treating a subject having a disease or condition associated with abnormal Toll-like receptor 3 as well as Toll-like receptor 4 and/or TLR3/TLR4 signaling in nonimmune cells, monocytes, macrophages, and/or dendritic cells in association with related pathologies. The present invention also relates to the treatment of autoimmune-inflammatory pathologies and chemokine and cytokine-mediated diseases associated with TLR overexpression and signaling. This invention also relates to pharmaceutical formulations capable of inhibiting the IRF-3/Type 1 IFN/STAT/ISRE/IRF-1 pathway associated with Toll-like receptor overexpression or signaling.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(co-treatment with; use of phenylmethimazoles, methimazole derivs., and tautomeric cyclic thiones for treatment of autoimmune/inflammatory diseases associated with toll-like receptor overexpression)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, co-treatment with; use of phenylmethimazoles, methimazole derivs., and tautomeric cyclic thiones for treatment of autoimmune/inflammatory diseases associated with toll-like receptor overexpression)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 6 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:451474 CAPLUS
DOCUMENT NUMBER: 141:1258
TITLE: Nitrosated compounds in methods of treating vascular diseases characterized by nitric oxide insufficiency
INVENTOR(S): Loscalzo, Joseph; Vita, Joseph A.; Loberg, Michael D.;

	Worcel, Manuel
PATENT ASSIGNEE(S):	USA
SOURCE:	U.S. Pat. Appl. Publ., 23 pp., Cont.-in-part of U.S. Ser. No. 679,257.
	CODEN: USXXCO
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	5
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004105850	A1	20040603	US 2003-692724		20031027
US 6635273	B1	20031021	US 2000-697317		20001027
US 2004071766	A1	20040415	US 2003-679257		20031007
PRIORITY APPLN. INFO.:			US 1999-162230P	P	19991029
			US 2000-179020P	P	20000131
			US 2000-697317	A1	20001027
			US 2003-679257	A2	20031007

OTHER SOURCE(S): MARPAT 141:1258

AB The invention provides methods of treating and/or preventing vascular diseases characterized by nitric oxide insufficiency by administering a therapeutically effective amount of at least one nitrosated angiotensin-converting enzyme inhibitor, nitrosated beta-adrenergic blocker, nitrosated cholesterol reducer, nitrosated calcium channel blocker, nitrosated endothelin antagonist, nitrosated angiotensin II receptor antagonist, nitrosated renin inhibitor, and optionally at least one compound used to treat cardiovascular diseases and/or at least one antioxidant, or a pharmaceutically acceptable salt thereof, and/or at least one compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. The antioxidant may preferably be a hydralazine compound or a pharmaceutically acceptable salt thereof. The compound that donates, transfers or releases nitric oxide, elevates endogenous levels of endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase may preferably be isosorbide dinitrate and/or isosorbide mononitrate. The vascular diseases characterized by nitric oxide insufficiency include a cardiovascular disease and a disease resulting from oxidative stress. Nitric oxide action was shown to be impaired in the microvasculature of black hypertensive patients to a greater extent than in white hypertensive patients.

IT **9028-35-7D**, HMG-CoA reductase, nitrosated compds.
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitrosated compds. in methods of treating vascular diseases characterized by nitric oxide insufficiency)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 7 OF 36 MEDLINE on STN

ACCESSION NUMBER:	2005540355 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 16002570
TITLE:	**Simvastatin** inhibits cigarette smoking-induced emphysema and **pulmonary hypertension** in rat **lungs**.
AUTHOR:	Lee Ji-Hyun; Lee Dong-Soon; Kim Eun-Kyung; Choe Kang-Hyeon; Oh Yeon-Mock; Shim Tae-Sun; Kim Sang-Eun; Lee Yun-Song; Lee Sang-Do

CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine, Pochon CHA University, Seongnam, Korea.
SOURCE: American journal of respiratory and critical care medicine, (2005 Oct 15) Vol. 172, No. 8, pp. 987-93. Electronic Publication: 2005-07-07.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200601
ENTRY DATE: Entered STN: 12 Oct 2005
Last Updated on STN: 7 Jan 2006
Entered Medline: 6 Jan 2006

AB RATIONALE: In cigarette smoking-induced chronic obstructive **pulmonary** disease, structural and functional derangements are characterized by parenchymal destruction and **pulmonary hypertension**. Statins are 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase inhibitors that have been used as lipid-lowering agents. These drugs also have additional pharmacologic properties, including antiinflammation, scavenging reactive oxygen species, restoring endothelial function, and antithrombogenesis, all of which can counteract the harmful effects of cigarette smoking. OBJECTIVE: We performed assays to determine whether **simvastatin** could attenuate **lung** damage induced by chronic cigarette smoking in rats. METHODS: In Sprague-Dawley rats exposed to cigarette smoke for 16 weeks, morphologic changes in the **lungs** and **pulmonary** arterial pressure were examined. MAIN RESULTS: **Simvastatin** inhibited **lung** parenchymal destruction and development of **pulmonary hypertension**, and also inhibited peribronchial and perivascular infiltration of inflammatory cells and induction of matrix metalloproteinase-9 activity in **lung** tissue. **Simvastatin** additionally prevented **pulmonary** vascular remodeling and the changes in endothelial nitric oxide synthase expression induced by smoking. In human **lung** microvascular endothelial cells, **simvastatin** increased expression of endothelial nitric oxide synthase mRNA. CONCLUSIONS: **Simvastatin** ameliorated the structural and functional derangements of the **lungs** caused by cigarette smoking, partly by suppressing inflammation and matrix metalloproteinase-9 induction and preventing **pulmonary** vascular abnormality. These findings indicate that statins may play a role in the treatment of cigarette smoking-induced chronic obstructive **pulmonary** disease.

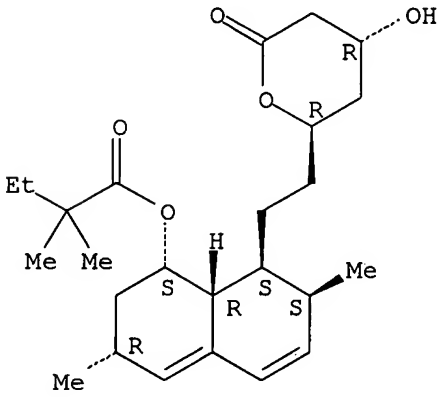
L16 ANSWER 8 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1997:800788 CAPLUS
DOCUMENT NUMBER: 128:123608
TITLE: Inhibition of 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase
AUTHOR(S): Laufs, Ulrich; La Fata, Vito; Liao, James K.
CORPORATE SOURCE: Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (1997), 272(50), 31725-31729
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypoxia induces vasoconstriction, in part, by down-regulating endothelial cell nitric oxide synthase (ecNOS) expression. Previous studies indicate

that 3-hydroxy-3-methylglutaryl-CoA (HMG CoA) reductase inhibitors improve endothelium-dependent relaxation by increasing ecNOS activity. To determine whether HMG CoA reductase inhibitors can prevent hypoxia-mediated down-regulation of ecNOS function and expression, human endothelial cells were exposed to hypoxia (3% O2) in the presence of HMG CoA reductase inhibitors **simvastatin** and lovastatin for various durations (0-48 h). Hypoxia decreased ecNOS protein and mRNA levels in a time-dependent manner, resulting in a 4- and 9-fold reduction after 48 h, resp. In a concentration-dependent manner, **simvastatin**, and to a lesser extent, lovastatin, prevented the down-regulation of ecNOS expression by hypoxia. **Simvastatin**-induced changes in ecNOS expression correlated with changes in endothelial NO production and were reversed by treatment with L-mevalonate. Actinomycin D studies revealed that under hypoxic conditions, **simvastatin** increased ecNOS mRNA half-life from 13 to 38 h. Nuclear run-on studies showed that **simvastatin** had no effect on repression of ecNOS gene transcription by hypoxia. These results indicate that HMG CoA reductase inhibitors regulate ecNOS function and expression through changes in ecNOS mRNA stability and suggest that treatment with HMG CoA reductase inhibitors may have beneficial effects in patients with hypoxia-mediated **pulmonary hypertension**.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase blocks hypoxia-mediated down-regulation of endothelial nitric oxide synthase)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 9 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:688128 CAPLUS

DOCUMENT NUMBER: 133:247311
TITLE: Upregulation of type III endothelial cell nitric oxide synthase by HMG-CoA reductase inhibitors, and therapeutic use
INVENTOR(S): Liao, James K.; Laufs, Ulrich; Endres, Matthias; Moskowitz, Michael A.
PATENT ASSIGNEE(S): The Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 76 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056403	A1	20000928	WO 2000-US7221	20000317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2368187	AA	20000928	CA 2000-2368187	20000317
EP 1175246	A1	20020130	EP 2000-916511	20000317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2005038102	A1	20050217	US 2003-688721	20031015
PRIORITY APPLN. INFO.:			US 1999-273445 A	19990319
			US 1997-62093P P	19971014
			US 1998-132848 A2	19980811
			WO 2000-US7221 W	20000317

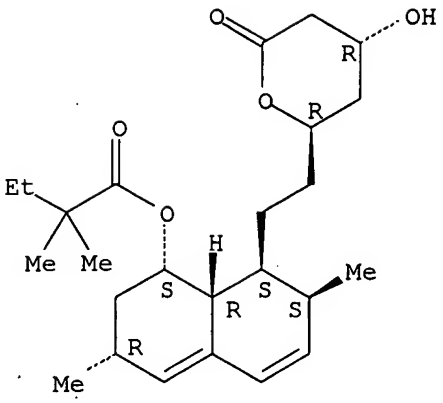
AB A new use for HMG-CoA reductase inhibitors is provided. In the invention, HMG-CoA reductase inhibitors are found to upregulate endothelial cell nitric oxide synthase activity through a mechanism other than preventing the formation of oxidative-LDL. As a result, HMG-CoA reductase inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell nitric oxide synthase. Such conditions include **pulmonary hypertension**, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG-CoA reductase inhibitor for upregulation of endothelial cell NO synthase, and therapeutic use)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HMG-CoA reductase inhibitor for upregulation of endothelial cell NO synthase, and therapeutic use)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 10 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:265880 CAPLUS
DOCUMENT NUMBER: 130:306590
TITLE: Upregulation of type III endothelial cell nitric oxide synthase by HMG-CoA reductase inhibitors
INVENTOR(S): Liao, James K.; Laufs, Ulrich; Endres, Matthias; Moskowitz, Michael A.
PATENT ASSIGNEE(S): Brigham & Women's Hospital, Inc., USA; The General Hospital Corporation
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9918952	A1	19990422	WO 1998-US21464	19981009
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6147109	A	20001114	US 1998-132848	19980811
CA 2307929	AA	19990422	CA 1998-2307929	19981009
AU 9896934	A1	19990503	AU 1998-96934	19981009
EP 1023060	A1	20000802	EP 1998-951041	19981009
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001519388	T2	20011023	JP 2000-515587	19981009
US 2005038102	A1	20050217	US 2003-688721	20031015

PRIORITY APPLN. INFO.: US 1997-62093P P 19971014
US 1998-132848 A 19980811
WO 1998-US21464 W 19981009
US 1999-273445 A1 19990319

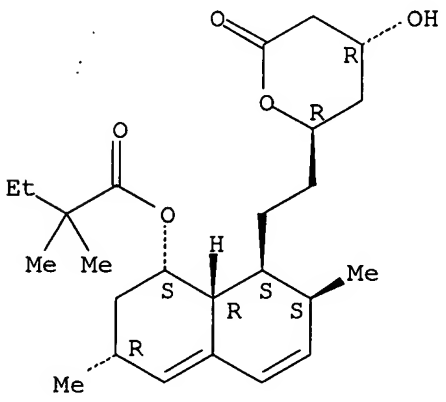
AB A new use for HMG-CoA reductase inhibitors is provided. In the invention, HMG-CoA reductase inhibitors are found to upregulate endothelial cell nitric oxide synthase activity through a mechanism other than preventing the formation of oxidative-LDL. As a result, HMG-CoA reductase inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell nitric oxide synthase. Such conditions include **pulmonary hypertension**, ischemic stroke, impotence, heart failure, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG-CoA reductase inhibitors for upregulation of type III endothelial cell nitric oxide synthase, and therapeutic use)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(HMG-CoA reductase inhibitors for upregulation of type III endothelial cell nitric oxide synthase, and therapeutic use)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 11 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2002661532 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12406854
TITLE: **Simvastatin** attenuates smooth muscle neointimal proliferation and **pulmonary hypertension** in rats.
AUTHOR: Nishimura Toshihiko; Faul John L; Berry Gerald J; Vaszar

Laszlo T; Qiu Daoming; Pearl Ronald G; Kao Peter N
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, and Department of Pathology, Stanford University Medical Center, Stanford, California 94305, USA.
CONTRACT NUMBER: AI39624 (NIAID)
HL62588 (NHLBI)
SOURCE: American journal of respiratory and critical care medicine, (2002 Nov 15) Vol. 166, No. 10, pp. 1403-8. Electronic Publication: 2002-08-15.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 8 Nov 2002
Last Updated on STN: 9 Jan 2003
Entered Medline: 8 Jan 2003

AB Hypertensive **pulmonary** vascular disease is characterized by abnormal proliferation of vascular endothelial and smooth muscle cells, leading to occlusion of **pulmonary** arterioles, **pulmonary hypertension**, right ventricular failure, and death. Compounds with antiproliferative effects on vascular endothelial and smooth muscle cells, such as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, may prevent the development of experimental hypertensive **pulmonary** vascular disease. Pneumonectomized rats injected with monocrotaline at 7 days develop severe hypertensive **pulmonary** vascular disease with neointimal formation. Rats were randomized to receive either vehicle or treatment with the HMG-CoA reductase inhibitor **simvastatin** (2 mg/kg per day). By Day 35, rats that received vehicle had higher mean **pulmonary** arterial pressures (53 +/- 2 mm Hg) and right ventricular hypertrophy (right ventricle/[left ventricle plus septum] [RV/LV+S] = 0.78 +/- 0.09) than rats in Group PMS5-35 that received **simvastatin** from Day 5 to 35 (mean **pulmonary** arterial pressure = 27 +/- 3 mm Hg, RV/LV+S = 0.34 +/- 0.08; $p < or = 0.001$). **Pulmonary** vascular remodeling with neointimal formation consisting of vascular smooth muscle cells was more severe in vehicle-treated rats (vascular occlusion score, 1.98 +/- 0.02) than in Group PMS5-35 (vascular occlusion score, 0.59 +/- 0.46; $p < 0.001$). In addition, **lung** endothelial nitric oxide synthase gene expression was decreased in vehicle-treated animals but was restored toward normal levels in **simvastatin**-treated animals. **Simvastatin** attenuates monocrotaline-induced **pulmonary** vascular remodeling with neointimal formation, **pulmonary** arterial **hypertension**, and right ventricular hypertrophy in rats.

L16 ANSWER 12 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2003455395 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12963647
TITLE: **Simvastatin** rescues rats from fatal **pulmonary hypertension** by inducing apoptosis of neointimal smooth muscle cells.
AUTHOR: Nishimura Toshihiko; Vaszar Laszlo T; Faul John L; Zhao Guohua; Berry Gerald J; Shi Lingfang; Qiu Daoming; Benson Gail; Pearl Ronald G; Kao Peter N
CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Stanford University Medical Center, Stanford, Calif 94305-5236, USA.
CONTRACT NUMBER: AI-39624 (NIAID)
HL-62588 (NHLBI)
SOURCE: Circulation, (2003 Sep 30) Vol. 108, No. 13, pp. 1640-5. Electronic Publication: 2003-09-08.
Journal code: 0147763. E-ISSN: 1524-4539.
PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200310
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 11 Oct 2003
Entered Medline: 10 Oct 2003

AB BACKGROUND: **Pulmonary** vascular injury by toxins can induce neointimal formation, **pulmonary** arterial **hypertension** (PAH), right ventricular failure, and death. We showed previously that **simvastatin** attenuates smooth muscle neointimal proliferation and **pulmonary hypertension** in pneumonectomized rats injected with the alkaloid toxin monocrotaline. The present study was undertaken to investigate the efficacy of **simvastatin** and its mechanism of reversing established neointimal vascular occlusion and **pulmonary hypertension**. METHODS AND RESULTS: Pneumonectomized rats injected with monocrotaline at 4 weeks demonstrated severe PAH at 11 weeks (mean **pulmonary** artery pressure [mPAP]=42 versus 17 mm Hg in normal rats) and death by 15 weeks. When rats with severe PAH received **simvastatin** (2 mg x kg(-1) x d(-1) by gavage) from week 11, there was 100% survival and reversal of PAH after 2 weeks (mPAP=36 mm Hg) and 6 weeks (mPAP=24 mm Hg) of therapy. **Simvastatin** treatment reduced right ventricular hypertrophy and reduced proliferation and increased apoptosis of pathological smooth muscle cells in the neointima and medial walls of **pulmonary** arteries. Longitudinal transcriptional profiling revealed that **simvastatin** downregulated the inflammatory genes fos, jun, and tumor necrosis factor-alpha and upregulated the cell cycle inhibitor p27Kip1, endothelial nitric oxide synthase, and bone morphogenetic protein receptor type 1a. CONCLUSIONS: **Simvastatin** reverses **pulmonary** arterial neointimal formation and PAH after toxic injury.

L16 ANSWER 13 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:338762 CAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of determining individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

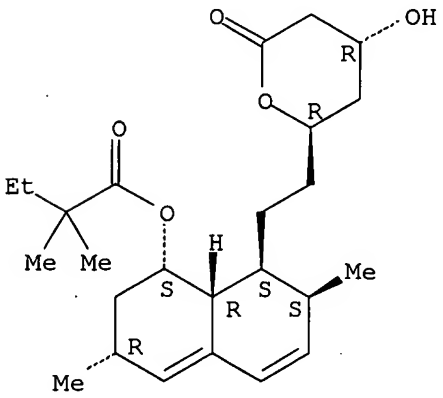
PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to determine the hypersensitivity of

individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7,** HMG CoA reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(methods of determining individual hypersensitivity to a pharmaceutical agent
from gene expression profile)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 14 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:679307 CAPLUS
DOCUMENT NUMBER: 145:124344
TITLE: Preparation of bicyclooctanecarboxamides as modulators of the glucocorticoid receptor, AP-1, and/or

NF-κB activity and use thereof

INVENTOR(S): Yang, Bingwei V.; Doweyko, Lidia M.; Doweyko, Arthur M.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 28 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

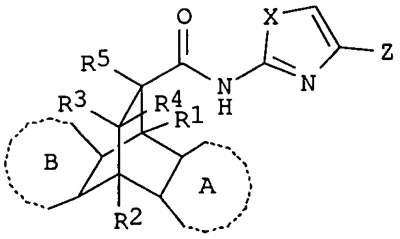
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006154975	A1	20060713	US 2006-330748	20060112
WO 2006076633	A1	20060720	WO 2006-US1329	20060113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

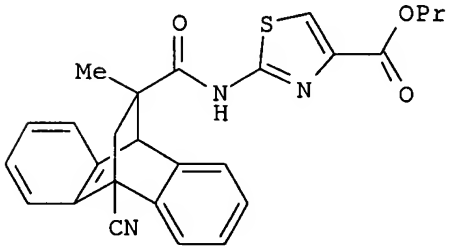
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-643462P P 20050113
US 2006-330748 A 20060112

GI



I



II

AB Title compds. I [X = S, O, or NH; Z = TCO2R6 or TCOR6; T = bond or (un)substituted alkylene; R1 and R2 independently = H, halo, OH, alkyl, etc.; R3 and R4 independently = H, alkyl, alkenyl, etc.; R5 = H, alkyl, alkynyl, aryl, etc.; R6 = alkyl, alkenyl, alkoxy, aryl, etc.; ring A and ring B independently represent (un)saturated 6-membered carbocycle or heterocyclic rings], and their pharmaceutical salts, are prepared and

disclosed as a class of novel nonsteroidal compds. which are useful in treating diseases associated with modulation of the glucocorticoid receptor, AP-1, and/or NF-κB activity including obesity, diabetes, inflammatory and immune diseases. Thus, e.g., II was prepared by coupling of the corresponding acid (preparation given) with Pr 2-aminothiazole-4-carboxylate. Methods for assaying glucocorticoid receptor inhibition (>25% at 10 M, preferably >95% at 10 M) and/or AP-1 inhibition activity (EC < 15 M) are described. Also provided are pharmaceutical compns. and methods of treating obesity, diabetes and inflammatory or immune-associated diseases comprising said compds.

IT **9028-35-7**, HMG CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of bicyclooctanecarboxamides as modulators of glucocorticoid receptor, AP-1, and/or NF-κB activity)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

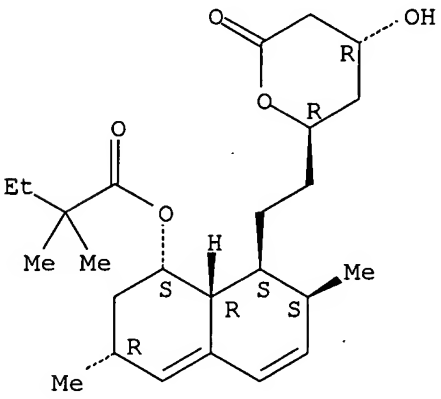
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of bicyclooctanecarboxamides as modulators of glucocorticoid receptor, AP-1, and/or NF-κB activity)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 15 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:679180 CAPLUS
DOCUMENT NUMBER: 145:145429
TITLE: Preparation of bicyclooctanecarboxamides as modulators of glucocorticoid receptor, AP-1 and NF-κB activity and use thereof
INVENTOR(S): Sheppeck, James; Dhar, T. g. Murali; Doweyko, Lidia; Gilmore, John; Weinstein, David; Xiao, Hai-Yun; Yang, Bingwei V.; Doweyko, Arthur M.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 71 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

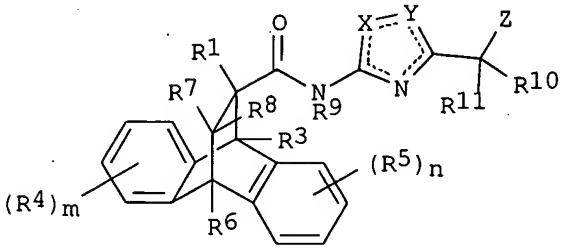
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006154973	A1	20060713	US 2006-330553	20060112
WO 2006076632	A1	20060720	WO 2006-US1328	20060113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

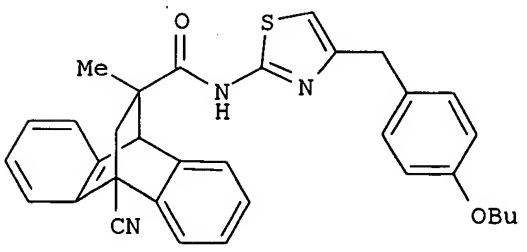
PRIORITY APPLN. INFO.:

US 2005-643509P	P	20050113
US 2006-330553	A	20060112

GI



I



II

AB Title compds. I [X = N, NH, O, and S; Y = N, NH, or CR2; R1 = H, CN, OH, alkyl, etc.; R2 = H, halo, OH, alkenyl, etc.; R3 and R6 independently = H, halo, alkoxy, aryl, etc.; R4 and R5 independently = H, alkyl, aryl, cycloalkyl, etc.; R7 and R8 independently = H, alkoxy, heteroaryl, etc.; R9 = H or alkyl; R10 and R11 independently = H, halo, alkynyl, etc.; Z = cycloalkyl, cycloalkenyl, heterocycloalkyl, aryl, or heteroaryl; m = 0-2; n = 0-2], and their pharmaceutically acceptable salts, are prepared and disclosed as useful in treating diseases associated with modulation of the glucocorticoid receptor, AP-1, and/or NF-κB activity including obesity, diabetes, inflammatory- and immune-associated diseases. Thus, e.g., I was prepared by alkylation of correponding alc. (preparation given) with 4-iodobutane. Methods for assaying glucocorticoid receptor inhibition (>25% at 10 M, preferably >95% at 10 M) and/or AP-1 inhibition activity (EC < 15 M) are described. Also provided are pharmaceutical compns. and methods of treating obesity, diabetes and inflammatory or immune-associated diseases comprising said compds.

IT **9028-35-7**, HMG CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of bicyclooctanecarboxamides as modulators of glucocorticoid receptor, AP-1 and NF-κB activity)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

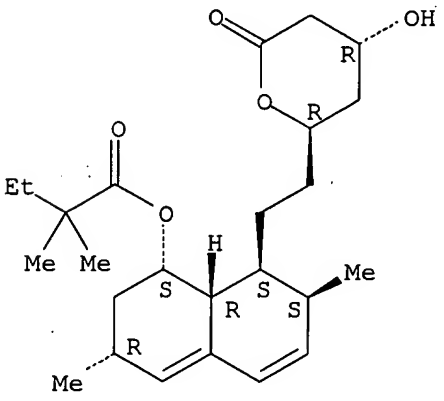
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of bicyclooctanecarboxamides as modulators of glucocorticoid receptor, AP-1 and NF-κB activity)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 16 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:678383 CAPLUS

DOCUMENT NUMBER: 145:124343

TITLE: Preparation of dibenzobicyclo[2.2.2]octadienylcarboxamides as modulators of the glucocorticoid receptor, ap-1, and/or NF-kb activity and use thereof

INVENTOR(S): Yang, Bingwei V.

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 33 pp.

CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

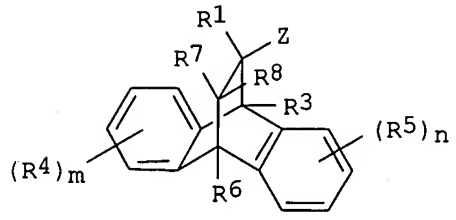
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006154962	A1	20060713	US 2006-330511	20060112
WO 2006076509	A1	20060720	WO 2006-US1117	20060113

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

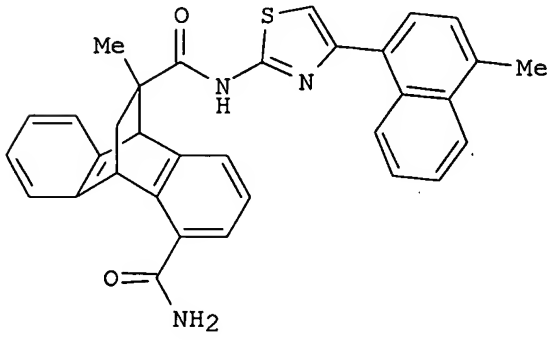
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-643760P P 20050113

GI



I



II

AB Title compds. I [R1 = H, OH, alkyl, etc.; R3 and R6 independently = H, halo, OH, alkyl, alkenyl, etc.; R7 and R8 independently = H, alkynyl, aryl, etc.; R4 and R5 independently = OH, alkoxy, aryloxy, etc.; Z = S(O)tNR1R2, CONR1R2 or CH2NR1R2 wherein R1 and R2 independently = H, alkyl, alkenyl, alkynyl, heteroaryl, etc.; m and n independently = 0-4 provided m+n ≥ 1; t = 1-2], and their pharmaceutically acceptable salts, are prepared and disclosed as novel non-steroidal compds. which are useful in treating diseases associated with modulation of the glucocorticoid receptor, AP-1, and/or NF-κB activity including obesity, diabetes, inflammatory and immune diseases. Thus, e.g., II was prepared by coupling

of the corresponding acid (preparation given) with 4-(4-methylnaphthalen-1-yl)thiazol-2-ylamine. Methods for assaying glucocorticoid receptor inhibition (>25% at 10 μM, preferably >95% at 10 μM) and/or AP-1 inhibition activity (EC50 < 15 μM) are described. Also provided are pharmaceutical compns. and methods of treating obesity, diabetes and inflammatory or immune associated diseases comprising said compds.

IT **9028-35-7**, HMG CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of dibenzobicyclo[2.2.2]octadienylcarboxamide derivs. as modulators of glucocorticoid receptor, AP-1 and/or NF-κB activity)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

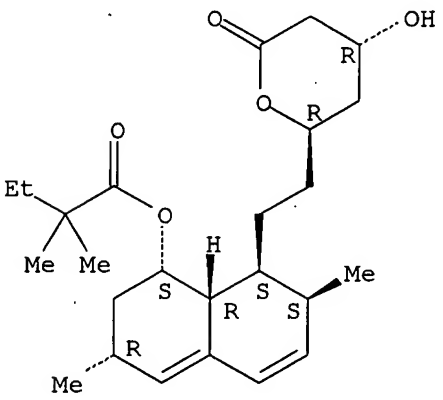
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of dibenzobicyclo[2.2.2]octadienylcarboxamide derivs. as modulators of glucocorticoid receptor, AP-1 and/or NF-κB activity)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 17 OF 36 MEDLINE on STN

ACCESSION NUMBER: 2003413999 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12750068

TITLE: Attenuation of chronic hypoxic **pulmonary hypertension** by **simvastatin**.

AUTHOR: Girgis Reda E; Li Dechun; Zhan Xinhua; Garcia Joe G N; Tuder Rubin M; Hassoun Paul M; Johns Roger A

CORPORATE SOURCE: Division of Pulmonary and Critical Care Medicine, Department of Medicine, Johns Hopkins University, 1830 E. Monument, 5th Floor, Baltimore, MD 21205, USA.. rgirgis@jhmi.edu

SOURCE: American journal of physiology. Heart and circulatory physiology, (2003 Sep) Vol. 285, No. 3, pp. H938-45. Electronic Publication: 2003-05-15. Journal code: 100901228. ISSN: 0363-6135.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200309
ENTRY DATE: Entered STN: 5 Sep 2003
Last Updated on STN: 28 Sep 2003
Entered Medline: 26 Sep 2003

AB The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been shown to improve multiple normal endothelial cell functions and inhibit vascular wall cell proliferation. We hypothesized that one such agent, **simvastatin**, would attenuate chronic hypoxic **pulmonary hypertension**. Male adult Sprague-Dawley rats were exposed (14 days) to normoxia (N), normoxia plus once-a-day administered **simvastatin** (20 mg/kg ip) (NS), hypoxia (10% inspired O2 fraction) (H), or hypoxia plus **simvastatin** (HS). Mean **pulmonary** artery pressure, measured in anesthetized, ventilated rats with an open-chest method, was reduced from 25 +/- 2 mmHg in H to 18 +/- 1 in HS ($P < 0.001$) but did not reach normoxic values (12 +/- 1 mmHg). Similarly, right ventricular/left ventricular plus interventricular septal weight was reduced from 0.53 +/- 0.02 in the H group to 0.36 +/- 0.02 in the HS group ($P < 0.001$). The increased hematocrit in H (0.65 +/- 0.02) was prevented by **simvastatin** treatment (0.51 +/- 0.01, $P < 0.001$). Hematocrit was similar in N versus NS. Alveolar vessel muscularization and medial thickening of vessels 50-200 microM in diameter induced by hypoxia were also significantly attenuated in the HS animals. **Lung** endothelial nitric oxide synthase (eNOS) protein expression in the HS group was less than H ($P < 0.01$) but was similar in N versus NS. We conclude that **simvastatin** treatment potently attenuates chronic hypoxic **pulmonary hypertension** and polycythemia in rats and inhibits vascular remodeling. Enhancement of **lung** eNOS expression does not appear to be involved in mediating this effect.

L16 ANSWER 18 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:696690 CAPLUS
DOCUMENT NUMBER: 143:186790
TITLE: Fused aryl and heteroaryl bicyclo[2.2.2]octane derivative modulators of the glucocorticoid receptor, AP-1, and/or NF-κB activity, and therapeutic use thereof
INVENTOR(S): Duan, Jingwu; Jiang, Bin; Sheppeck, James; Gilmore, John L.
PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

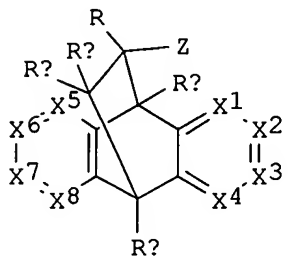
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005070207	A1	20050804	WO 2005-US1411	20050114

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2005176716	A1	20050811	US 2005-34652	20050113
EP 1705990	A1	20061004	EP 2005-711524	20050114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, TR, BG, CZ, EE, HU, PL, SK, HR, IS, YU				
PRIORITY APPLN. INFO.:			US 2004-537467P	P 20040116
			US 2005-34652	A 20050113
			WO 2005-US1411	W 20050114

OTHER SOURCE(S): MARPAT 143:186790

GI



I

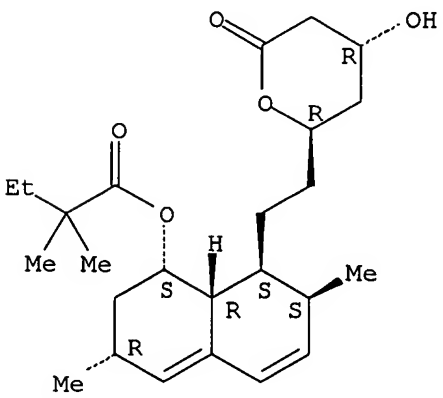
AB A class of non-steroidal compds. are provided which are useful in treating diseases associated with modulation of the glucocorticoid receptor, AP-1, and/or NF-κB activity including obesity, diabetes, inflammatory and immune diseases. The compds. of the invention are fused aryl and heteroaryl bicyclo[2.2.2]octane derivs. I [R = H, OH, alkyl, etc.; Ra, Rb = H, halo, OH, alkyl, etc.; Rc, Rd = H, alkyl, alkenyl, etc.; Z = S(O)tNR1R2, CONR1R2, CH2NR1R2; t = 1,2; R1, R2 = H, alkyl, etc.; X1-X8 = CR15, NR18, etc.; R15 = H, halo, OH, etc.; R18 = H, aryl, alkyl, etc.]. Also provided are pharmaceutical compns. and methods comprising the above compds. for treating obesity, diabetes and inflammatory or immune-associated diseases. Compound preparation is included.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fused aryl and heteroaryl bicyclo[2.2.2]octane derivative modulators of glucocorticoid receptor, AP-1, and/or NF-κB activity, and therapeutic use)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; fused aryl and heteroaryl bicyclo[2.2.2]octane derivative modulators of glucocorticoid receptor, AP-1, and/or NF-κB activity, and therapeutic use)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 19 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2005187020 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15821229
TITLE: **Simvastatin** treatment of **pulmonary hypertension**: an observational case series.
AUTHOR: Kao Peter N
CORPORATE SOURCE: Pulmonary and Critical Care Medicine, Stanford University Medical Center, Stanford, CA 94305-5236, USA.. peterkao@stanford.edu
SOURCE: Chest, (2005 Apr) Vol. 127, No. 4, pp. 1446-52.
Journal code: 0231335. ISSN: 0012-3692.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CASE REPORTS)
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200505
ENTRY DATE: Entered STN: 12 Apr 2005
Last Updated on STN: 1 Jun 2005
Entered Medline: 31 May 2005

AB BACKGROUND: Statins confer cardiovascular benefits beyond the reduction of serum cholesterol through antiproliferative and antiinflammatory mechanisms and induction of endothelial nitric oxide expression. In pneumonectomized rats injected with monocrotaline, **simvastatin** reversed established **pulmonary hypertension** and conferred a 100% survival advantage. STUDY OBJECTIVES: To evaluate the safety and efficacy of **simvastatin** for treatment of patients with **pulmonary** arterial **hypertension** (PAH). DESIGN: Open-label observational study performed at Stanford University Medical Center. Sixteen patients with primary and secondary causes of PAH, World Health Organization (WHO) classes I (n = 2), II (n = 4), III (n = 3), IV (n = 7), are described. **Simvastatin** was prescribed at 20 to 80 mg/d and continued in the absence of adverse effects. MEASUREMENTS AND RESULTS: Serial measurements of 6-min walk (6MW) performance, hemodynamics, and echocardiographic estimates of right ventricular systolic pressures (RVSPs) were recorded on each patient. **Simvastatin** treatment was not associated with hepatic dysfunction, muscle necrosis, or other adverse events. Individual patients demonstrated improvements in 6MW performance, improvements in cardiac output, or decreases in RVSP that may be attributable to **simvastatin** treatment. Overall, the rate of disease progression appeared to be attenuated, and WHO class IV patients demonstrated improved survival. CONCLUSIONS: **Simvastatin** treatment appears safe in patients with PAH.

L16 ANSWER 20 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:608478 CAPLUS
DOCUMENT NUMBER: 145:89971
TITLE: Pharmaceutical compositions comprising NEP inhibitors, inhibitors of the endogenous endothelin-producing

system and HMG-CoA reductase inhibitors

INVENTOR(S): Witte, Klaus; Ziegler, Dieter; Straub, Matthias; Koopman, Paulus Antonius Remigius

PATENT ASSIGNEE(S): Solvay Pharmaceuticals G.m.b.H., Germany

SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006064016	A1	20060622	WO 2005-EP56772	20051214
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006189595	A1	20060824	US 2005-302512	20051214
PRIORITY APPLN. INFO.:			EP 2004-106589 A	20041215
			US 2004-635963P P	20041215

OTHER SOURCE(S): MARPAT 145:89971

AB A novel combination therapy is described for cardiovascular and metabolic diseases or conditions, by administering a synergistic combination of at least one inhibitor of neutral endopeptidase (NEP), at least one inhibitor of the endogenous endothelin producing system, and at least one HMG-CoA reductase inhibitor. Thus, a randomized, placebo-controlled, parallel group, multicenter, single dose study of oral daglutril, a dually acting compound capable of inhibiting NEP and the endogenous endothelin producing system, during 12 h right heart catheterization in human subjects with congestive heart failure was performed. Administration of a HMG CoA reductase inhibitor (atorvastatin, atorvastatin calcium, pravastatin, pravastatin sodium or **simvastatin**) in addition to daglutril resulted in an addnl. and beneficial decrease in **pulmonary** blood pressure, when compared to the administration of daglutril as a monotherapy. Also, granules were produced containing daglutril calcium 200 mg, **simvastatin** 50 mg, corn starch 50 mg, and lactose 80 mg, mixed with talc 5 mg, magnesium stearate 5 mg and corn starch 10 mg, and filled into capsules.

IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; oral compns. comprising NEP inhibitors, inhibitors of endogenous endothelin-producing system and HMG-CoA reductase inhibitors for treatment of cardiovascular and metabolic diseases)

RN 9028-35-7 CAPLUS

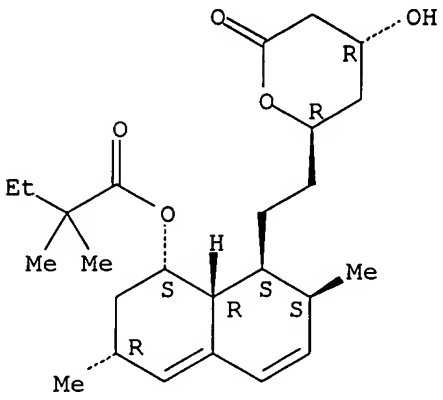
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(oral compns. comprising NEP inhibitors, inhibitors of endogenous endothelin-producing system and HMG-CoA reductase inhibitors for treatment of cardiovascular and metabolic diseases)

RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 21 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1995:746368 CAPLUS
DOCUMENT NUMBER: 123:132873
TITLE: HMG-CoA reductase inhibitors in the normalization of vascular endothelial dysfunction
INVENTOR(S): Hirsch, Laurence J., III; Boccuzzi, Stephen J.; Plotkin, Diane J.; Mitchel, Yale B.; Ganz, Peter; Creager, Mark A.; Alexander, R. Wayne
PATENT ASSIGNEE(S): Merck and Co., Inc., USA; Brigham and Women's Hospital, Inc.; Emory University
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 9513063	A1	19950518	WO 1994-US13068		19941109
W: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, UZ					
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
AU 9510956	A1	19950529	AU 1995-10956		19941109
PRIORITY APPLN. INFO.:			US 1993-149252	A	19931109
			WO 1994-US13068	W	19941109

AB Patients with or at risk of developing ischemic syndromes are treated with doses of an HMG-CoA reductase inhibitor to lower total and LDL cholesterol in order to restore endogenous vascular endothelium-dependent activities including, but not limited to vasodilatory responses modulating vascular tone and blood flow, anti-adherent properties of the blood vessel wall and anti-coagulation of platelets. The HMG-CoA reductase inhibitors include lovastatin, **simvastatin**, pravastatin, and fluvastatin.

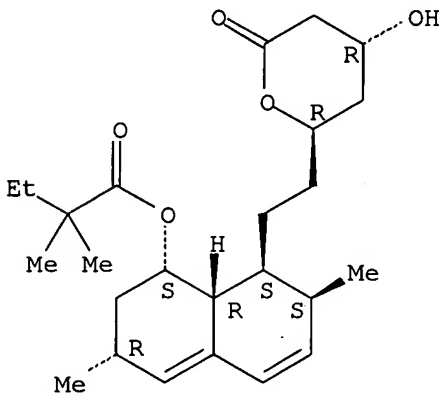
IT **79902-63-9, Simvastatin**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG-CoA reductase inhibitors for normalization of vascular endothelial dysfunction)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; HMG-CoA reductase inhibitors for normalization of vascular endothelial dysfunction)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

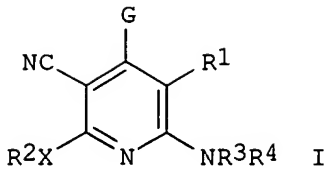
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 22 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2005:824492 CAPLUS
DOCUMENT NUMBER: 143:222525
TITLE: Method of using 3-cyano-4-arylpyridine derivatives as modulators of androgen receptor function, preparation thereof, and use with other agents
INVENTOR(S): Nirschl, Alexandra A.; Hamann, Lawrence G.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005182105	A1	20050818	US 2005-48437		20050201
PRIORITY APPLN. INFO.:			US 2004-541780P	P	20040204

OTHER SOURCE(S): MARPAT 143:222525
GI



I

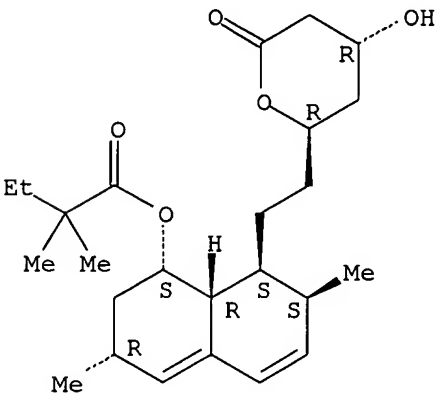
AB A method is provided for treating androgen receptor-associated conditions, such as age-related diseases, e.g. sarcopenia, employing a compound I [R1 = CN, H; X = O, S; R2 = (substituted) alkyl, (substituted) cycloalkyl, etc; R3, R4 = H, (substituted) alkyl, etc.; G = (substituted) aryl, (substituted) heteroaryl], or a pharmaceutically acceptable salt or prodrug ester thereof. Preparation of selected I is described. I may be used in combination with other agents.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyanoarylpyridine derivative modulators of androgen receptor function, preparation, and use with other agents)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; cyanoarylpyridine derivative modulators of androgen receptor function, preparation, and use with other agents)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 23 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2006533847 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16698853
TITLE: **Simvastatin** causes endothelial cell apoptosis and attenuates severe **pulmonary hypertension**
.
AUTHOR: Taraseviciene-Stewart Laimute; Scerbavicius Robertas; Choe Kang-Hyeon; Cool Carlyne; Wood Kathy; Tuder Rubin M; Burns Nana; Kasper Michael; Voelkel Norbert F

CORPORATE SOURCE: Division of Pulmonary Sciences and Critical Care Medicine, Department of Pathology, University of Colorado Health Sciences Center, Denver, CO 80262, USA.
CONTRACT NUMBER: 1P01-HL66254-01A1 (NHLBI)
SOURCE: American journal of physiology. Lung cellular and molecular physiology, (2006 Oct) Vol. 291, No. 4, pp. L668-76. Electronic Publication: 2006-05-12. Journal code: 100901229. ISSN: 1040-0605.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 9 Sep 2006
Last Updated on STN: 8 Nov 2006
Entered Medline: 7 Nov 2006

AB Severe **pulmonary hypertension** (SPH) is characterized by precapillary arteriolar lumen obliteration, dramatic right ventricular hypertrophy, and pericardial effusion. Our recently published rat model of SPH recapitulates major components of the human disease. We used this model to develop new treatment strategies for SPH. SPH in rats was induced using VEGF receptor blockade in combination with chronic hypoxia. A large variety of drugs used in this study, including anticancer drugs (cyclophosphamide and paclitaxel), the angiotensin-converting enzyme inhibitor lisinopril, the antiangiogenic agent thalidomide, and the peroxisome proliferator-actived receptor-gamma agonist PGJ2, failed to decrease mean **pulmonary** artery pressure (PAP) or right ventricular hypertrophy. In contrast, treatment of rats with established SPH with **simvastatin** markedly reduced mean PAP and right ventricular hypertrophy, and this reduction was associated with caspase-3 activation and **pulmonary** microvascular endothelial cell apoptosis. **Simvastatin** partially restored caveolin-1, caveolin-2, and phospho-caveolin expression in vessel walls. In rat primary **pulmonary** microvascular endothelial cells, **simvastatin** induced caspase 3 activation and Rac 1 expression while suppressing Rho A and attenuated levels of Akt and ERK phosphorylation. We conclude that **simvastatin** is effective in inducing apoptosis in hyperproliferative **pulmonary** vascular lesions and could be considered as a potential drug for treatment of human SPH.

L16 ANSWER 24 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:73535 CAPLUS
DOCUMENT NUMBER: 134:125966
TITLE: Upregulation of type III endothelial cell nitric oxide synthase by rho GTPase function inhibitors
INVENTOR(S): Liao, James K.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: U.S., 42 pp., Cont.-in-part of U.S. Ser. No. 92,618, abandoned. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6180597	B1	20010130	US 1998-132849	19980811
WO 9947153	A2	19990923	WO 1999-US6185	19990319
WO 9947153	A3	19991118		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,

JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9931075	A1	19991011	AU 1999-31075		19990319
PRIORITY APPLN. INFO.:			US 1998-78774P	P	19980319
			US 1998-92618	B2	19980605
			US 1998-132849	A	19980811
			WO 1999-US6185	W	19990319

AB A use for rho GTPase function inhibitors is provided. In the instant invention, rho GTPase function inhibitors are found to upregulate endothelial cell Nitric Oxide Synthase activity. As a result, rho GTPase function inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include **pulmonary hypertension**, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but do not necessarily exclude hyperlipidemics and hypercholesterolemics.

IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors of; upregulation of type III endothelial cell nitric oxide synthase by rho GTPase function inhibitors)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

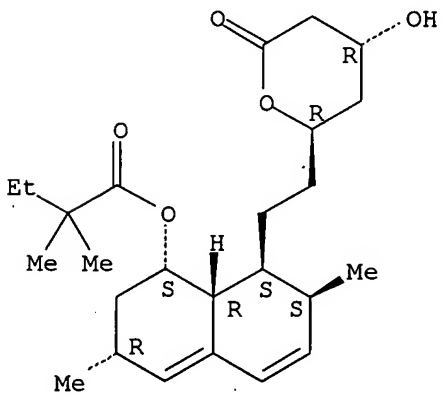
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(upregulation of type III endothelial cell nitric oxide synthase by rho GTPase function inhibitors)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 25 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:68368 CAPLUS
DOCUMENT NUMBER: 132:117563
TITLE: Upregulation of type III endothelial cell nitric oxide synthase by agents that disrupt actin cytoskeletal organization
INVENTOR(S): Liao, James K.
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000003746	A2	20000127	WO 1999-US15827	19990714
WO 2000003746	A3	20000420		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002082281	A1	20020627	US 1998-115387	19980714
US 6423751	B1	20020723		
AU 9949905	A1	20000207	AU 1999-49905	19990714
US 2003013703	A1	20030116	US 2002-144669	20020513
US 6696480	B2	20040224		

PRIORITY APPLN. INFO.:			
US 1998-115387	A	19980714
US 1999-273224	A	19990319
WO 1999-US15827	W	19990714

AB A use for agents that disrupt actin cytoskeletal organization is provided. In the instant invention, agents that disrupt actin cytoskeletal organization are found to upregulate endothelial cell Nitric Oxide Synthase activity. As a result, agents that disrupt actin cytoskeletal organization are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include **pulmonary hypertension**, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

IT **9028-35-7**, HMG-CoA reductase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(inhibitors; upregulation of type III endothelial cell nitric oxide synthase by agents that disrupt actin cytoskeletal organization)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

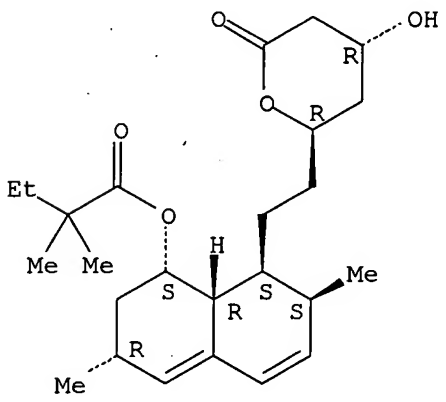
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(upregulation of type III endothelial cell nitric oxide synthase by agents that disrupt actin cytoskeletal organization)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 26 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1999:613683 CAPLUS

DOCUMENT NUMBER: 131:223519

TITLE: Upregulation of type III endothelial cell nitric oxide synthase by rho GTPase function inhibitors, and therapeutic use

INVENTOR(S): Liao, James K.

PATENT ASSIGNEE(S): Brigham & Women's Hospital, Inc., USA

SOURCE: PCT Int. Appl., 105 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9947153	A2	19990923	WO 1999-US6185	19990319
WO 9947153	A3	19991118		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6180597	B1	20010130	US 1998-132849	19980811
AU 9931075	A1	19991011	AU 1999-31075	19990319

PRIORITY APPLN. INFO.:

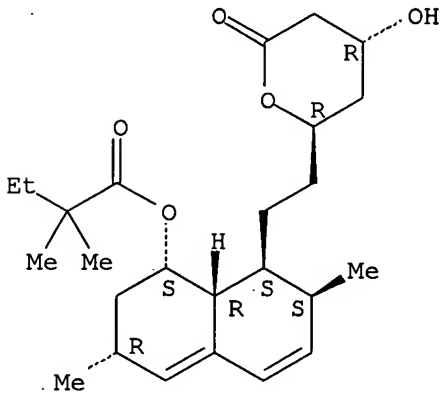
US 1998-78774P	P	19980319
US 1998-92618	A	19980605
US 1998-132849	A	19980811
WO 1999-US6185	W	19990319

AB A use for rho GTPase function inhibitors is provided. In the invention,

rho GTPase function inhibitors are found to upregulate endothelial cell Nitric Oxide Synthase activity. As a result, rho GTPase function inhibitors are useful in treating or preventing conditions that result from the abnormally low expression and/or activity of endothelial cell Nitric Oxide Synthase. Such conditions include **pulmonary hypertension**, ischemic stroke, impotence, heart failure, hypoxia-induced conditions, insulin deficiency, progressive renal disease, gastric or esophageal motility syndrome, etc. Subjects thought to benefit mostly from such treatments include nonhyperlipidemics and nonhypercholesterolemics, but not necessarily exclude hyperlipidemics and hypercholesterolemics.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(endothelial cell nitric oxide synthase upregulation with rho GTPase function inhibitors, and therapeutic use, alone or with other agents)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; endothelial cell nitric oxide synthase upregulation with rho GTPase function inhibitors, and therapeutic use, alone or with other agents)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 27 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:238842 CAPLUS
DOCUMENT NUMBER: 142:291452
TITLE: Modulating cell activity by using an agent that reduces the level of cholesterol within a cell
INVENTOR(S): Allen, Janet Marjorie; Overington, John Paul
PATENT ASSIGNEE(S): Inpharmatica Limited, UK
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005023305	A2	20050317	WO 2004-GB3875	20040910
WO 2005023305	A3	20050616		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 2003-21228 A 20030910

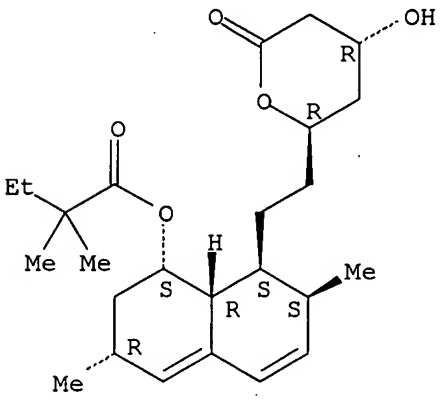
AB The invention discloses methods for modulating the activity of cells, and compns. useful in such methods. In particular, the invention relates to the use of an agent that reduces the level of cholesterol within a cell to modulate the activity of the cell, and to methods involving such use.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cell activity modulation with agent reducing level of cell cholesterol)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, statins; cell activity modulation with agent reducing level of cell cholesterol)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 28 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:367143 CAPLUS
DOCUMENT NUMBER: 144:412493

TITLE: Rhodanine derivatives as PPAR receptor modulators and their preparation, pharmaceutical compositions and use for treatment and prophylaxis of various diseases

INVENTOR(S): Sarshar, Sepehr; Marappan, Subrumanian
PATENT ASSIGNEE(S): Auspex Pharmaceuticals, Inc., USA

SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

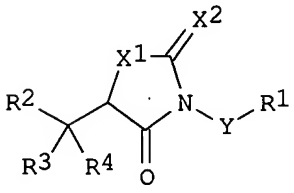
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006041921	A2	20060420	WO 2005-US35832	20051004

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

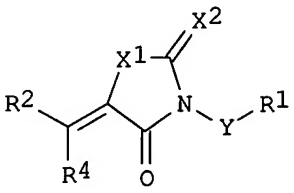
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-616574P P 20041005
OTHER SOURCE(S): MARPAT 144:412493

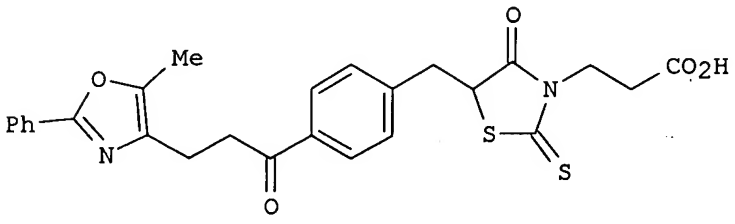
GI



I



II



III

AB Processes for the preparation of compds. of formulas I and II are described. These compds. can be used as PPAR modulators and for the treatment and/or management of cancer, inflammation, cellular differentiation and proliferation, wound healing, metabolism of lipids and carbohydrates, obesity, diabetes, and energy homeostasis. Compds. of formula I and II wherein X1 and X2 are independently O, S, or NH; Y is (un)substituted C1-10 alkyl; R1 is (un)substituted C5-11 oxocycloalkenyl, (R9CO)(R10CO)CH, or (un)substituted dioxodioxanyl; R9 and R10 are independently OH, alkoxyl, aryloxy, NH2, alkylamino, arylamino, N-aryl-N-alkylamino, -NHNH2, alkylhydrazino, arylhydrazino, N-aryl-N-alkylamino, NHOH and derivs.,

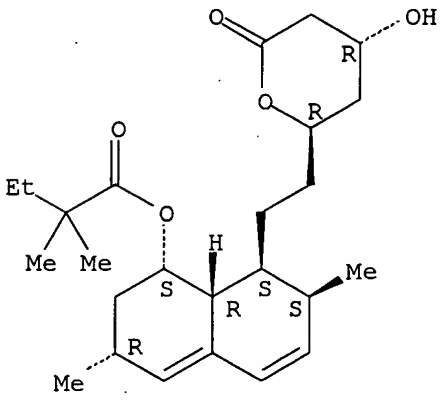
alkyl, or aryl; R2 and R3 are independently H, halo, or alkyl; R4 is substituted aryl and heteroaryl; and their pharmaceutically acceptable salts, and prodrugs thereof are claimed. Example compound III was prepared by addition of methyllithium to 4-(diethoxymethyl)benzaldehyde to give the corresponding alc., which was oxidized to give 4-(diethoxymethyl)acetophenone, which underwent acylation with di-Et carbonate; the resulting 2-[4-(diethoxymethyl)benzoyl]acetate underwent alkylation with 4-chloromethyl-5-methyl-2-phenyloxazole followed by decarboxylation to give 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propionyl]benzaldehyde, which underwent condensation with rhodanine-N-propionic acid to give 4-[3-(5-methyl-2-phenyl-4-oxazolyl)propionyl]benzylidene-3-(β-carboxyethyl)rhodanine, which underwent hydrogenation to give example compound III. The invention compds. were evaluated for their PPAR-γ modulating activity. From the assay, it was determined example compound III exhibited an EC50 0.127 μM.

IT **9028-35-7**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, statins; preparation of rhodanine derivs. as PPAR receptors modulators useful in treatment and prophylaxis of diseases)
RN 9028-35-7 CAPLUS
CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Zocor**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of rhodanine derivs. as PPAR receptors modulators useful in treatment and prophylaxis of diseases)
RN 79902-63-9 CAPLUS
CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 29 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:339390 CAPLUS
DOCUMENT NUMBER: 144:363144
TITLE: Method of prevention and treatment of aging and age-related disorders including atherosclerosis, peripheral vascular disease, coronary artery disease, osteoporosis, arthritis, type 2 diabetes, dementia, Alzheimer's disease and cancer
INVENTOR(S): Omoigui, Osemwota Sota
PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 59 pp., Cont.-in-part of U.S. Ser. No. 122,030.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006078533	A1	20060413	US 2005-268609	20051108
US 2006078531	A1	20060413	US 2004-961037	20041012
US 2006078532	A1	20060413	US 2005-122030	20050505
PRIORITY APPLN. INFO.:			US 2004-961037 A2	20041012
			US 2005-122030 A2	20050505

AB The invention relates to a method for prevention and treatment of aging and age-related disorders including atherosclerosis, peripheral vascular disease, coronary artery disease, osteoporosis, type 2 diabetes, dementia and some forms of arthritis and cancer in a subject comprising administering to said subject, sep., sequentially or simultaneously a therapeutically effective dosage of each component or combination of statins, bisphosphonates, cholesterol lowering agents or techniques, interleukin-6 inhibitor/antibody, interleukin-6 receptor inhibitor/antibody, interleukin-6 antisense oligonucleotide (ASON), gp130 protein inhibitor/antibody, tyrosine kinases inhibitors/antibodies, serine/threonine kinases inhibitors/antibodies, mitogen-activated protein (MAP) kinase inhibitors/antibodies, phosphatidylinositol 3-kinase (PI3K) inhibitors/antibodies, Nuclear factor κB (NF-κB) inhibitors/antibodies, IκB kinase (IKK) inhibitors/antibodies, activator protein-1 (AP-1) inhibitors/antibodies, STAT transcription factors inhibitors/antibodies, altered IL-6, partial peptides of IL-6 or IL-6 receptor, or SOCS (suppressors of cytokine signaling) protein, or a functional fragment thereof, administered sep., in sequence or simultaneously. Inhibition of the signal transduction pathway for Interleukin 6 mediated inflammation is key to the prevention and treatment of atherosclerosis, peripheral vascular disease, coronary artery disease, aging and age-related disorders including osteoporosis, type 2 diabetes, dementia and some forms of arthritis and tumors. Inhibition of Interleukin 6 mediated inflammation may be achieved indirectly through regulation of endogenous cholesterol synthesis and isoprenoid depletion or by direct inhibition of the signal transduction pathway utilizing interleukin-6 inhibitor/antibody, interleukin-6 receptor inhibitor/antibody, interleukin-6 antisense oligonucleotide (ASON), gp130 protein inhibitor/antibody, tyrosine kinases inhibitors/antibodies, serine/threonine kinases inhibitors/antibodies, mitogen-activated protein (MAP) kinase inhibitors/antibodies, phosphatidylinositol 3-kinase (PI3K) inhibitors/antibodies, Nuclear factor κB (NF-κB) inhibitors/antibodies, IκB kinase (IKK) inhibitors/antibodies, activator protein-1 (AP-1) inhibitors/antibodies, STAT transcription factors inhibitors/antibodies, altered IL-6, partial peptides of IL-6 or IL-6 receptor, or SOCS (suppressors of cytokine signaling) protein, or a functional fragment thereof. Said method for prevention and treatment of said disorders is based on inhibition of interleukin-6 inflammation through regulation of cholesterol metabolism, isoprenoid depletion and/or inhibition of the signal transduction pathway.

IT **9028-35-7**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitors, statins; method of prevention and treatment of aging and age-related disorders)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

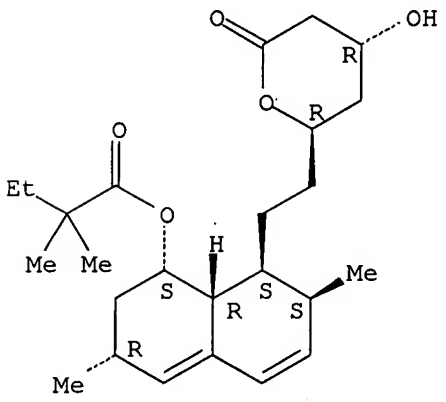
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method of prevention and treatment of aging and age-related disorders)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 30 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1997:397373 CAPLUS

DOCUMENT NUMBER: 127:13464

TITLE: Method and pharmaceutical compositions using ACAT inhibitors in combination with HMG-CoA-reductase inhibitors for regulating lipid concentration

INVENTOR(S): Bocan, Thomas M. A.

PATENT ASSIGNEE(S): Warner-Lambert Company, USA; Bocan, Thomas M. A.

SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9716184	A1	19970509	WO 1996-US15854	19961002
W: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KE, KR, LK, LR, LS, LT, LV, MG, MK, MN, MW, MX, NO, NZ, PL, RO, SD, SG, SI, SK, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2233558	AA	19970509	CA 1996-2233558	19961002
CA 2233558	C	20051206		
AU 9672539	A1	19970522	AU 1996-72539	19961002
AU 720853	B2	20000615		
EP 858336	A1	19980819	EP 1996-934020	19961002
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
CN 1201389	A	19981209	CN 1996-198010	19961002
BR 9611410	A	19990105	BR 1996-11410	19961002
JP 11515025	T2	19991221	JP 1997-517342	19961002
NZ 319906	A	20000228	NZ 1996-319906	19961002

IL 123902	A1	20030112	IL 1996-123902		19961002
NZ 512484	A	20030228	NZ 1996-512484		19961002
PL 186714	B1	20040227	PL 1996-326365		19961002
SK 284142	B6	20041005	SK 1998-557		19961002
CN 1679953	A	20051012	CN 2005-10051723		19961002
RO 120816	B1	20060830	RO 1998-919		19961002
ZA 9609187	A	19970529	ZA 1996-9187		19961031
US 6124309	A	20000926	US 1998-51368		19980407
BG 64018	B1	20031031	BG 1998-102417		19980429
NO 9801961	A	19980504	NO 1998-1961		19980430
HK 1016509	A1	20060324	HK 1999-101732		19990421
US 6093719	A	20000725	US 1999-345944		19990701
US 6143755	A	20001107	US 1999-346503		19990701
PRIORITY APPLN. INFO.:			US 1995-6155P	P	19951102
			CN 1996-198010	A3	19961002
			WO 1996-US15854	W	19961002

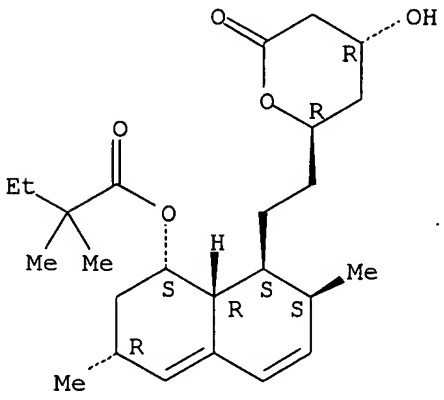
AB The present invention concerns a combination of an ACAT inhibitor, for example, [(2,4,6,-tris(1-methylethyl)phenyl)acetyl]sulfamic acid 2,6-bis(1-methylethyl)phenyl ester, and an HMG-CoA-reductase inhibitor, for example, atorvastatin, effective for lipid regulation. The drug combination results in a greater reduction of plasma VLDL and LDL cholesterol and increase of HDL cholesterol than either drug alone, the result of which is a less atherogenic lipoprotein profile. The combination is useful in the treatment of patients with or at risk of developing ischemic syndromes.

IT **79902-63-9, Simvastatin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACAT inhibitors in combination with HMG-CoA-reductase inhibitors used as hypolipidemic and antiatherosclerotic drugs in ischemic syndromes)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; ACAT inhibitors in combination with HMG-CoA-reductase inhibitors used as hypolipidemic and antiatherosclerotic drugs in ischemic syndromes)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 31 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2006037198 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16423196
TITLE: **Pulmonary** arterial **hypertension**: new insights and new hope.
AUTHOR: Martin Kevin B; Klinger James R; Rounds Sharon I S
CORPORATE SOURCE: Pulmonary & Critical Care, Department of Medicine, Brown Medical School, Providence VA Medical Center, Providence, RI, USA.
SOURCE: Respirology (Carlton, Vic.), (2006 Jan) Vol. 11, No. 1, pp. 6-17. Ref: 92
Journal code: 9616368. ISSN: 1323-7799.
PUB. COUNTRY: Australia
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200606
ENTRY DATE: Entered STN: 21 Jan 2006
Last Updated on STN: 21 Jun 2006
Entered Medline: 20 Jun 2006

AB **Pulmonary** arterial **hypertension** (PAH) is a devastating disorder characterized by abnormal increased vasoconstriction and vascular remodelling. In this review we discuss the pathophysiology, genetic basis and clinical features of this disorder. Current therapy of PAH is based on an understanding of its pathogenesis, and we review current treatment options based on the pathophysiology of the disease. We discuss three promising novel therapies studied in animal models and human tissue. All three therapies appear to prevent and reduce **pulmonary** arterial medial hyperplasia through their anti-proliferative and/or pro-apoptotic effects: serotonin transporter inhibitors by blocking serotonin uptake; dichloroacetate by activating voltage-gated potassium channels; and **simvastatin** by preventing activation of small GTPases.

L16 ANSWER 32 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:473238 CAPLUS
DOCUMENT NUMBER: 141:1260
TITLE: Materials and methods for monitoring vascular endothelial function, and use in monitoring vascular therapy
INVENTOR(S): Segal, Mark S.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 17 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2004110241	A1	20040610	US 2002-313435	20021206
PRIORITY APPLN. INFO.:			US 2002-313435	20021206

AB The invention discloses a method for monitoring a patient's vascular endothelial function by obtaining a test blood specimen from the patient; measuring the amount of circulating endothelial cells (CECs), endothelial progenitor cells (EPCs), or both within the test blood specimen; and determining the state of activation of CECs and/or EPCs within the test blood specimen. The invention also discloses methods for monitoring responsiveness to vascular therapy, e.g. a statin-based therapy, using the quantity and surface phenotype of CECs and/or EPCs as diagnostic or

prognostic indicators of vascular health, and particularly vascular endothelial health, before, during, or after the vascular therapy.

IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; vascular endothelial function monitoring, and use in monitoring vascular therapy)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

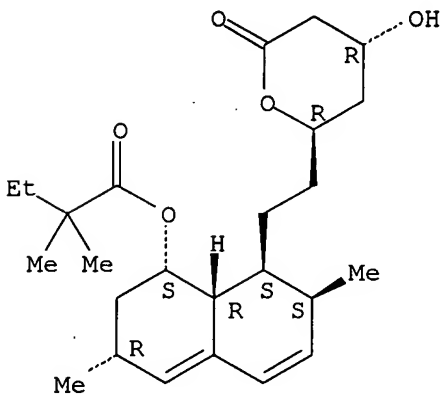
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vascular endothelial function monitoring, and use in monitoring vascular therapy)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L16 ANSWER 33 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:903746 CAPLUS
DOCUMENT NUMBER: 136:42836
TITLE: HMG CoA reductase inhibitors for promoting angiogenesis
INVENTOR(S): Walsh, Kenneth
PATENT ASSIGNEE(S): St. Elizabeth's Medical Center of Boston, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001093806	A2	20011213	WO 2001-US18175	20010605
WO 2001093806	A3	20020418		
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
US 6689807	B1	20040210	US 2000-590740	20000608
CA 2411396	AA	20011213	CA 2001-2411396	20010605

AU 2001075256	A5	20011217	AU 2001-75256		20010605
EP 1286702	A2	20030305	EP 2001-941945		20010605
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR					
US 2004122077	A1	20040624	US 2003-713678		20031114
PRIORITY APPLN. INFO.:			US 2000-590740	A	20000608
			WO 2001-US18175	W	20010605

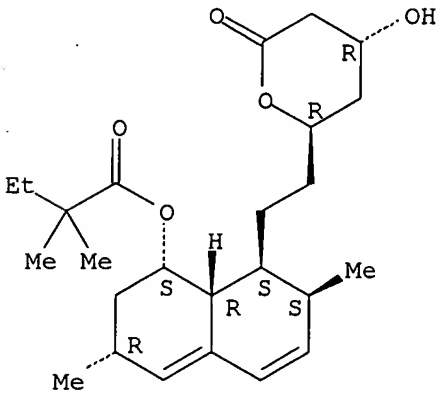
AB This invention relates to methods and compns. for the treatment of conditions associated with vascular insufficiency, and to methods and compns. for screening assays to select agents that are useful for this purpose. In particular the invention relates to HMG CoA reductase inhibitors and their use in promoting angiogenesis in vivo and in activating Akt in vascular endothelial cells in vitro and in vivo.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMG CoA reductase inhibitors for promoting angiogenesis)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; HMG CoA reductase inhibitors for promoting angiogenesis)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 34 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	2004:41320 CAPLUS
DOCUMENT NUMBER:	140:87743
TITLE:	Therapeutic use and pharmaceutical compositions of cholesterol ester transfer protein (CETP) inhibitors and optional HMG-CoA reductase inhibitors and/or antihypertensive agents
INVENTOR(S):	Nguyen, Tu Trung; Shear, Charles Lester; Revkin, James Harold; Ruggeri, Roger Benjamin
PATENT ASSIGNEE(S):	Pfizer Products Inc., USA
SOURCE:	PCT Int. Appl., 159 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
WO 2004004778	A1	20040115	WO 2003-IB2792		20030618
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
US 2004053842	A1	20040318	US 2003-459683		20030610
CA 2488736	AA	20040115	CA 2003-2488736		20030618
AU 2003244921	A1	20040123	AU 2003-244921		20030618
EP 1519754	A1	20050406	EP 2003-738394		20030618
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK					
BR 2003012421	A	20050419	BR 2003-12421		20030618
CN 1665537	A	20050907	CN 2003-815575		20030618
JP 2005532388	T2	20051027	JP 2004-519080		20030618
NO 2005000497	A	20050308	NO 2005-497		20050128
PRIORITY APPLN. INFO.:			US 2002-393395P	P	20020702
			US 2002-393395	P	20020702
			WO 2003-IB2792	W	20030618

OTHER SOURCE(S): MARPAT 140:87743

AB The invention discloses cholesterol ester transfer protein (CETP) inhibitors, pharmaceutical compns. containing such inhibitors, and the use of such inhibitors to treat certain diseases/conditions, optionally in combination with certain therapeutic agents e.g., antihypertensive agents.

IT **9028-35-7**, HMG-CoA reductase
RL: BSU (Biological study, unclassified); BIOL (Biological study) (therapeutic use and pharmaceutical compns. of cholesterol ester transfer protein inhibitors and optional HMG-CoA reductase inhibitors and/or antihypertensive agents)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

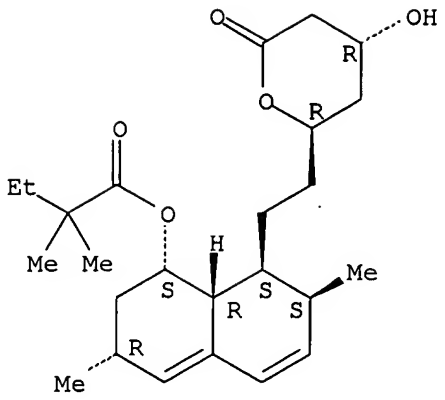
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic use and pharmaceutical compns. of cholesterol ester transfer protein inhibitors and optional HMG-CoA reductase inhibitors and/or antihypertensive agents)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 35 OF 36 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:952876 CAPLUS
DOCUMENT NUMBER: 145:328380
TITLE: Combination therapy for endothelial dysfunction, angina and diabetes
INVENTOR(S): Kaesemeyer, Wayne
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006205727	A1	20060914	US 2006-373658	20060310
WO 2006099244	A1	20060921	WO 2006-US8801	20060310

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2005-660625P P 20050311
US 2005-675118P P 20050427

AB The combination of a HMG CoA reductase inhibitor like a statin, such as **simvastatin**, with a pFox inhibitor such as trimetazidine ("Simetazidine") is particularly advantageous for treatment of end-stage complications, such as acute coronary syndrome (ACS) and chronic angina, especially in type II diabetics. The combination therapy is also useful in the treatment and/or prevention of chronic heart failure (CHF) and peripheral arterial disease (PAD). The combination of a nitric oxide (NO) mechanism with increased NO production with pFox inhibition simultaneously treats both the effect and the cause of angina. One or more oral hypoglycemic compds. (biguanides, insulin sensitizers, such as thiazolidinediones, α-glucosidase inhibitors, insulin secretagogues, and dipeptidyl peptidase IV inhibitors), protein kinase C (PKC) inhibitors, and

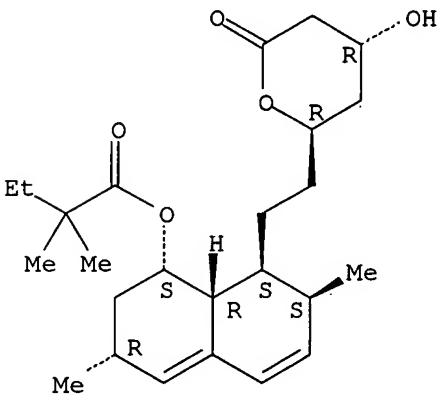
acetyl-CoA carboxylase inhibitors can also be used in combination with the HMG CoA reductase inhibitors and/or pFox inhibitors, especially in type II diabetics, to control glucose levels and treat endothelial dysfunction. The drugs can be given in combination (e.g. a single tablet) or in sep. dosage forms, administered simultaneously or sequentially. In the preferred form the statin is given in a dose of between 5 and 80 mg/day in two sep. doses, and the pFox inhibitor is administered in a sustained or extended dosage formulation at a dose of 20 mg three times a day or 35 mg two times a day. The dose of the oral hypoglycemic, PKC inhibitor, or acetyl-CoA carboxylase inhibitor varies with the type of drug used.

IT **79902-63-9, Simvastatin**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for endothelial dysfunction, angina and diabetes)

RN 79902-63-9 CAPLUS

CN Butanoic acid, 2,2-dimethyl-, (1S,3R,7S,8S,8aR)-1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-[(2R,4R)-tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl]ethyl]-1-naphthalenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **9028-35-7**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors, statins; combination therapy for endothelial dysfunction, angina and diabetes)

RN 9028-35-7 CAPLUS

CN Reductase, hydroxymethylglutaryl coenzyme A (reduced nicotinamide adenine dinucleotide phosphate) (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L16 ANSWER 36 OF 36 MEDLINE on STN
ACCESSION NUMBER: 2002661536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12421739
TITLE: Therapy of **pulmonary hypertension**: the evolution from vasodilators to antiproliferative agents.
AUTHOR: Rubin Lewis J
SOURCE: American journal of respiratory and critical care medicine, (2002 Nov 15) Vol. 166, No. 10, pp. 1308-9.
Journal code: 9421642. ISSN: 1073-449X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Commentary
Editorial
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200301

ENTRY DATE: Entered STN: 8 Nov 2002
Last Updated on STN: 9 Jan 2003
Entered Medline: 8 Jan 2003

=>

patch, nor does it require energy from ATP hydrolysis to unfold. The reported rise in the level of oxidized proteins in the diaphragm of the ventilated rats (3) could, therefore, explain the need to augment 20S proteasome activity.

The development of oxidative stress in limb muscles has been observed after more than 4 days of disuse and was associated with increased lipid peroxidation and a reduction in total glutathione (6). The reported rise in protein carbonyls and 8-isoprostane in the diaphragm after only 18 hours of controlled mechanical ventilation is rather surprising. Controlled mechanical ventilation causes a special form of disuse because the diaphragm is being passively shortened by repeated lung inflations. Passive muscle shortening increases blood flow and affects muscle metabolism (7), which might partly explain the different time course of oxidative stress in the diaphragm versus limb muscles. The mechanisms of ventilator-induced oxidative stress were not explored by Shanely and coworkers (3). Limb muscle studies revealed, however, that disuse is associated with a significant upregulation of superoxide-generating xanthine oxidase (8) and elevated levels of transition metals, including iron, calcium, copper, and manganese (6). The rise in iron is expected to facilitate the generation of hydroxyl radicals from superoxide and hydrogen peroxide. Moreover, manganese and copper are capable of catalyzing the oxidation of glutathione, thereby reducing the overall antioxidant capacity.

The possible rise in intracellular calcium in the diaphragm of ventilated rats could explain the observed increase in muscle calpain activity. One major consequence of augmented calpain activity would be the partial disorganization of the highly ordered intact myofibrils that are normally, unlike its individual constituent actin and myosin, resistant to proteasome proteolysis (5). Furthermore, the fact that an inhibitor of calpains (E-64d) also attenuated ventilator-induced proteolysis (3), suggests that calpain activity is required to render muscle proteins amenable to degradation by the proteasome.

Is the human diaphragm as susceptible to ventilator-induced cachexia as the diaphragm of the rat? This question has not yet been answered. We speculate on the basis that the rate of disuse muscle atrophy correlates strongly and positively with body mass–specific metabolic rate (which is higher in rats than in humans) (9) and that relatively longer periods of mechanical ventilation than those reported in the study of Shanely and coworkers are required to produce disuse atrophy in humans.

What could be done to prevent controlled mechanical ventilation-induced diaphragm atrophy? When feasible, modes of partial ventilator support allowing diaphragmatic contractions are an attractive, although unproven, alternative. The results of Shanely and coworkers, however, point to another possibility. Antioxidant supplementation could prevent the development of oxidative stress and consequently attenuate muscle proteolysis. This proposal is supported by the observations that vitamin E supplements attenuate immobilization-induced atrophy in limb muscles (6). In fact, this is what occurs when hibernating animals are immobilized for prolonged periods of time, yet muscle atrophy doesn't develop. This is because of a decrease in metabolic rate (and hence reduction in oxygen radical formation) and a concomitant rise in the expression of antioxidant enzymes (10). An additional useful intervention that warrants testing is the prevention of the rise in intracellular calcium with dantrolene (5). Finally, future development of tissue-specific proteasome and calpain inhibitors might ameliorate disuse atrophy.

SABAH N. A. HUSSAIN, M.D.
THEODOROS VASSILAKOPOULOS, M.D.
Meakins-Christie Laboratories
McGill University
Montreal, Quebec, Canada

References

1. Vassilakopoulos T, Zakynthinos S, Roussos C. Respiratory muscles and weaning failure. *Eur Respir J* 1996;9:2383–2400.
2. Le Bourdelles G, Viires N, Boczkowski J, Seta N, Pavlovic D, Aubier M. Effects of mechanical ventilation on diaphragmatic contractile properties in rats. *Am J Respir Crit Care Med* 1994;149:1539–1544.
3. Shanely RA, Zergeroglu MA, Lennon SL, Sugiura T, Yimlamai T, Enns D, Belcastro A, Powers SK. Mechanical ventilation–induced diaphragmatic atrophy is associated with oxidative injury and increased proteolytic activity. *Am J Respir Crit Care Med* 2002;166:1369–1374.
4. Carafoli E, Molinari M. Calpain: a protease in search of a function? *Biochem Biophys Res Commun* 1998;247:193–203.
5. Hasselgren PO, Fischer JE. Muscle cachexia: current concepts of intracellular mechanisms and molecular regulation. *Ann Surg* 2001;233:9–17.
6. Kondo H, Miura M, Nakagaki I, Sasaki S, Itokawa Y. Trace element movement and oxidative stress in skeletal muscle atrophied by immobilization. *Am J Physiol* 1992;262:E583–E590.
7. Holmang A, Mimura K, Lonnroth P. Involuntary leg movements affect interstitial nutrient gradients and blood flow in rat skeletal muscle. *J Appl Physiol* 2002;92:982–988.
8. Kondo H, Nakagaki I, Sasaki S, Hori S, Itokawa Y. Mechanism of oxidative stress in skeletal muscle atrophied by immobilization. *Am J Physiol* 1993;265:E839–E844.
9. Hudson NJ, Franklin CE. Maintaining muscle mass during extended disuse: aestivating frogs as a model species. *J Exp Biol* 2002;205:2297–2303.
10. Grundy JE, Storey KB. Antioxidant defenses and lipid peroxidation damage in estivating toads: Scaphiopus couchii. *J Comp Physiol [B]* 1998;168:132–142.

DOI: 10.1164/rccm.2208004

Therapy of Pulmonary Hypertension

The Evolution from Vasodilators to Antiproliferative Agents

Nearly 50 years ago, Paul Wood observed that intravenous acetylcholine produced an acute reduction in pulmonary artery pressure in a patient with pulmonary artery hypertension (PAH) and postulated that a "vasoconstrictive factor" was involved in pathogenesis (1). Early approaches to therapy for pulmonary arterial hypertension were based on this concept and consisted of the administration of a variety of systemic vasodilators that also reduced pulmonary vascular resistance in some patients. The pathologic changes of pulmonary hypertension, however, whether idiopathic or associated with connective tissue diseases, congenital heart disease, human immunodeficiency virus infection, or other conditions typically consist of more extensive changes than simple hyperplasia of the smooth muscle layer and include intimal fibrosis and myointimal proliferation. Accordingly, it is not surprising that although some patients experience clinical and hemodynamic improvement with "pure" vasodilator agents, the vast majority of patients with PAH manifest little or no benefit from these drugs. Indeed, vasodilators can produce hypotension, worsening intrapulmonary gas exchange, depressed cardiac function, and even death when more advanced vasculopathy predominates over vasoconstriction (2).

Our understanding of the factors involved in the pathogenesis of PAH has evolved dramatically over the past decade and has led to the development of newer therapeutic strategies that target these processes. For example, the demonstration that the hypertensive pulmonary endothelium is deficient in its production of prostacyclin (3, 4) led to the development of continuous intravenous prostacyclin therapy (5)—the first treatment for PAH approved by the Food and Drug Administration. Nonparenteral alternative delivery modes of prostanoid therapy have now been used successfully (6, 7) and may ultimately replace the complex but highly effective intravenous route of administration. The finding that the hypertensive pulmonary endothelium overexpresses endothelin, a potent vasoconstrictor and mitogen (8), served as the rationale for investigating the endothelin receptor antagonist bosentan in PAH (9), the second drug approved by the Food and Drug Administration for this condition. Although prostacyclin is a vasodilator, its long-term therapeutic effects in PAH, as with bosentan, are exerted primarily through its antiproliferative properties (10). Accordingly, the absence of an acute vasodilator response to prostacyclin or other vasodilator, such as inhaled nitric oxide, implies that chronic vasodilator therapy is contraindicated and that chronic antiproliferative therapy with bosentan or a prostanoid is the treatment approach of choice.

In this issue of *AJRCCM*, Nishimura and coworkers (pp. 1403–1408) report that simvistatin, an 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA)-reductase inhibitor (statin), attenuates the vascular injury and remodeling in an animal model of PAH produced by monocrotaline and pneumonectomy (11). Animals treated with simvistatin at the induction of vascular injury manifested the most substantial effect, with near-preservation of hemodynamics, vascular morphology, and endothelial function assessed by endothelial nitric oxide gene expression. The responses to simvistatin were attenuated but were still present when it was administered 2 weeks after the induction of vascular injury. The authors conclude that statins may be of benefit in the treatment of PAH as a pulmonary vascular antiproliferative agent. The pleiotropic or cholesterol-independent effects of statins have been investigated extensively in systemic arteries and may be related to the ability of statins to inhibit the synthesis of isoprenoid intermediates that are involved in intracellular signaling processes, thereby restoring endothelial function, inhibiting smooth muscle cell proliferation, and stimulating angiogenesis (12).

Although clinicians who care for patients with PAH may be tempted to simply add a statin to the treatment of patients with PAH based on the study by Nishimura and colleagues, I believe that it is premature to do so for several reasons. First, although the animal model employed in these studies develops a pulmonary arteriopathy that is pathologically similar to that seen in human PAH, it is unclear whether these pathogenic pathways are similar or disparate; unlike the monocrotaline/pneumonectomy model, in which the injury is induced acutely, the pathogenic process in PAH is dynamic. Accordingly, the arteriopathy in PAH may be less responsive to interventions, particularly when the disease process is long-standing and advanced. Second, the incorporation of new treatments into the armamentarium should be based on results from well-designed and carefully performed clinical trials that demonstrate convincing evidence of both safety and efficacy. Finally, information regarding optimal dosing and potential interactions with other agents that are used to treat PAH are currently limited, and these data are critical before embarking on a course of treatment with any drug.

As efforts continue to develop more effective therapies for PAH, it is clear that there will be no "magic bullet" that completely reverses the vasculopathy in all cases. Clinical trials designed to target several parallel pathogenic pathways, such as combinations of prostanoids with endothelin receptor blockers or phosphodiesterase inhibitors, are currently in development in the belief that the beneficial effects of these drugs will be additive (13), as has been the case with this strategy in other disorders such as congestive heart failure. The report by Nishimura and coworkers provides encouraging support, but not proof, for a novel approach to antiproliferative therapy for PAH using statins, agents that are already in the marketplace and readily available. Although it is unlikely that statin therapy alone will be of substantial benefit in advanced PAH, the effects of the addition of a statin to other established therapies are worthy of further investigation.

LEWIS J. RUBIN, M.D.
University of California, San Diego, La Jolla, California

References

1. Wood P. Pulmonary hypertension with special reference to the vasoconstrictive factor. *Br Heart J* 1959;21:557.
2. Rubin LJ. Current concepts: primary pulmonary hypertension. *N Engl J Med* 1997;336:111–117.
3. Tuder RM, Cool CD, Geraci MW, Wang J, Abman SH, Wright L, Badesch D, Voelkel NF. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am J Respir Crit Care Med* 1999;159:1925–1932.
4. Christman BW, McPherson CD, Newman JH, King GA, Bernard GR, Groves BM, Loyd JE. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N Engl J Med* 1992;327:70–75.
5. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Tapson VF, Clayton LM, Crow JW. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension: PPH Study Group. *N Engl J Med* 1996;334:296–301.
6. Olschewski H, Higenbottam TW, Naeije R, Simonneau G, Galie N, Rubin LJ, Nikkho S, Speich R, Hoeper MM, Behr J, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002;347:322–329.
7. Galie N, Humbert M, Vacchiery JL, Vizza CD, Kneussl M, Manes A, Sitbon O, Torbicki A, Delcroix M, Naeije R, *et al.* Effects of beroprost sodium, an oral prostacyclin analogue in patients with pulmonary arterial hypertension in a randomized double blind placebo controlled trial. *J Am Coll Cardiol* 2002;39:1496–1502.
8. Giaid A, Yanagisawa M, Langleben D, Michel RP, Levy R, Shennib H, Kimura S, Masaki T, Duguid WP, Stewart DJ. Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993;328:1732–1739.
9. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.
10. Clapp LH, Finney P, Turcato S, Tran S, Rubin LJ, Tinker A. Differential effects of stable prostacyclin analogues on smooth muscle proliferation and cyclic AMP generation in human pulmonary artery. *Am J Respir Cell Mol Biol* 2002;26:194–201.
11. Nishimura T, Faul JL, Berry GJ, Vaszar LT, Qiu D, Pearl RG, Kao PN. Simvastatin attenuates smooth muscle neointimal proliferation and pulmonary hypertension in rats. *Am J Respir Crit Care Med* 2002;166:1403–1408.
12. Liao JK. Isoprenoids as mediators of the biological effects of statins. *J Clin Invest* 2002;110:285–288.
13. Hoeper M, Galie N, Simonneau G, Rubin LJ. Pulmonary perspective: new treatments for pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2002;165:1209–1216.

DOI: 10.1164/rccm.2208008